

Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

**ALAN R. KATRITZKY, FRS**

*Kenan Professor of Chemistry*

*Department of Chemistry*

*University of Florida*

*Gainesville, Florida*



**ACADEMIC PRESS**

---

An imprint of Elsevier Science

**Volume 84**

Amsterdam Boston London New York Oxford Paris  
San Diego San Francisco Singapore Sydney Tokyo

# Contributors

*Numbers in parantheses indicate the pages on which the author's contributions begin.*

**Nadia M. Ahmad** (1), Department of Chemistry, Imperial College of Science, Technology and Medicine, Exhibition Road, London, SW7 2AY, UK

**El-Sayed H. El-Ashry** (71), Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

**István Hermecz** (219), Chinoin Pharmaceutical and Chemical Works, Ltd., Research Center, Budapest, Hungary

**El-Sayed I. Ibrahim** (71), Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

**Jie Jack Li** (1), Department of Chemistry, Pfizer Global Research and Development, 2800 Plymouth Rd., Ann Arbor, MI 48105, USA

**Alexander P. Sadimenko** (191), Department of Chemistry, University of Fort Hare, 6 Chatham Road, Baysville, East London 5241, Republic of South Africa

**H.C. van der Plas** (31), Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB, Wageningen, The Netherlands

## *Editorial Advisory Board*

- A. T. Balaban, *Bucharest, Romania*  
M. Begtrup, *Copenhagen, Denmark*  
A. J. Boulton, *Norwich, England*  
J. Elguero, *Madrid, Spain*  
A. P. Krapcho, *Burlington, Vermont*  
E. Lukevics, *Riga, Latvia*  
A. P. Marchand, *Denton, Texas*  
V. I. Minkin, *Rostov-on-Don, Russia*  
C. A. Ramsden, *Keele, England*  
C. W. Rees, FRS, *London, England*  
J. Schantl, *Innsbruck, Austria*  
E. F. V. Scriven, *Indianapolis, Indiana*  
B. Stanovnik, *Ljubljana, Slovenia*  
Y. Yamamoto, *Sendai, Japan*  
J. A. Zoltewicz, *Gainesville, Florida*

## Preface

In the first chapter, N. M. Ahmad and J. J. Li (Pfizer, Ann Arbor, USA) discuss the use of palladium in quinoline synthesis, thus filling an important gap in a recent monograph on the uses of palladium catalysis in heterocyclic synthesis authored by the same group. This is followed by an account of pyrimidine-pyridine interconversions by H. C. van der Plas (Wageningen University, The Netherlands); the immense variety of heterocyclic chemistry is illustrated by the large number of diverse strategies for such transformations.

“Fused Heterocyclo-Quinolines Containing One Nitrogen Atom at the Ring Junction” is the subject of a chapter by E. H. El-Ashry and E. I. Ibrahim of Alexandria and Ismailia Universities, Egypt. This forms Part I of a series dealing with 4- and 5-membered heterocyclo-quinolines, compounds of increasing pharmaceutical interest, which have not previously been comprehensively reviewed. The series by A. P. Sadimenko (Fort Hare University, South Africa) on organometallic compounds of heterocycles is continued with a chapter concerning chalcogenoazoles and their benzannulated derivatives.

The final chapter by István Hermecz (Chinoin, Ltd., Budapest, Hungary) deals with bicyclic systems containing one ring junction nitrogen and one heteroatom and their benzologs, i.e. pyrido-oxazines, pyrido-thiazines, pyrido-pyridazines, pyrido-pyrazines, pyrido-pyrimidines and their analogs. Much of this material has not been reviewed for forty years, during which time immense advances have occurred.

ALAN R. KATRITZKY  
Department of Chemistry  
University of Florida  
PO Box 117200  
Gainesville, FL 32611



# Palladium in Quinoline Synthesis

NADIA M. AHMAD<sup>1</sup> AND JIE JACK LI<sup>2</sup>

*Department of Chemistry, Pfizer Global Research and Development,  
2800 Plymouth Rd., Ann Arbor, MI 48105, USA*

I. Introduction	1
II. Synthesis of Quinoline Electrophiles	2
A. Halogenation of Quinolones	2
B. Direct Halogenation of Quinolines	4
C. S <sub>N</sub> Ar Reaction	5
D. Halogen-dance Reaction	6
E. Vilsmeier–Haack Reaction	6
F. Miscellaneous Syntheses of Haloquinolines	7
III. Synthesis of Quinoline Nucleophiles	8
IV. Cross-coupling Reactions with Organometallic Reagents	10
A. Negishi Coupling	10
B. Suzuki Coupling	12
C. Stille Coupling	14
D. Hiyama Coupling	18
V. Sonagashira Reaction	20
VI. Heck Reaction	22
A. Intermolecular Heck Reaction	22
B. Intramolecular Heck Reaction	24
VII. Miscellaneous Reactions Mediated by Palladium	25
A. Oxidative Cyclization	25
B. Heteroannulation	25
C. Cyanation	26
D. Homocoupling	26
E. Phosphination	27
References	28

## I. Introduction

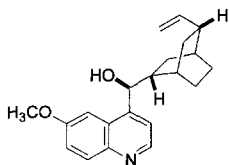
In 1803, William H. Wollaston discovered palladium from the crude platinum ore in London. He named it in honor of the newly detected

<sup>1</sup>Current address: Department of Chemistry, Imperial College of Science, Technology and Medicine, Exhibition Road, London, SW7 2AY, UK.

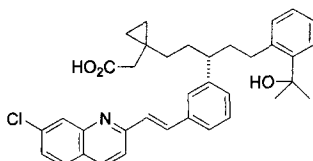
<sup>2</sup>E-mail: jack.li@pfizer.com

asteroid *Pallas*, which signifies the Greek goddess of wisdom. During most of the last two centuries, applications of palladium in organic chemistry have been virtually limited to catalytic hydrogenation and dehydrogenation. However, the last two decades have witnessed a crescendo of novel methodologies that efficiently create C–C, C–N and C–O bonds by employing catalytic palladium reagents.

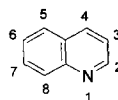
Quinolines play an indispensable role in medicinal chemistry. Quinine (**1**) is one of the oldest medicines used to fight malaria, whereas one of the latest quinoline-containing drugs is montelukast (**2**, Singulair®), an anti-asthmatic drug. Thus quinoline chemistry has always attracted the attention of medicinal chemists. Moreover, a recent book “Palladium in Heterocyclic Chemistry”, authored by Jack Li and Gordon Gribble, did not cover palladium in quinoline synthesis. To fill the void, in this chapter, we highlight important preparation methods of the quinoline substrates both as electrophiles and nucleophiles and their synthetic utilities in palladium-mediated reactions. The unique characteristics of quinoline chemistry stem from the stereoelectronic effects that the nitrogen atom has exerted on the quinoline molecule. Quinoline (**3**) is a  $\pi$ -electron-deficient heterocycle. Due to the electronegativity of the nitrogen atom, the  $\alpha$  and  $\gamma$  positions bear a partial positive charge, making these C(2) and C(4) positions prone to nucleophilic attacks. A similar trend occurs in the context of palladium chemistry. Halogens at the  $\alpha$  and  $\gamma$  positions of quinoline are more susceptible to oxidative addition to palladium(0) in comparison to simple carbocyclic aryl halides. As a consequence, even 2-chloro- and 4-chloro-quinolines undergo palladium-catalyzed reactions under standard conditions, a phenomenon not frequently observed in carbocyclic chloroaryl compounds.



1, quinine



2, montelukast

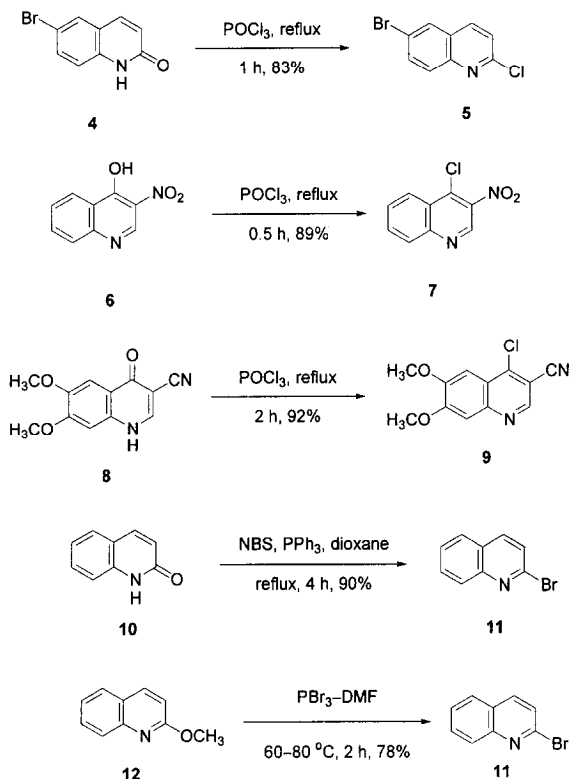


3, quinoline

## II. Synthesis of Quinoline Electrophiles

### A. HALOGENATION OF QUINOLONES

A popular method to prepare haloquinolines is the halogenation of quinolones using oxyphosphorus halides, most notably POCl<sub>3</sub>. The



Scheme 1

carbonyl can be located at either at the C(2) or the C(4) positions. As depicted in Scheme 1, the C(2) position of quinolone **4** was chlorinated with  $\text{POCl}_3$  to give 6-bromo-2-chloroquinoline (**5**) (2000EJMC931). The subsequent  $\text{S}_{\text{N}}\text{Ar}$  displacement of the chlorine substituent on **5** with sodium methoxide led to 6-bromo-2-methoxyquinoline. Analogously, chlorination at the C(4) position of quinolones is exemplified by transformations **6**  $\rightarrow$  **7** (91JMC1202) and **8**  $\rightarrow$  **9** (2000JMC3244).

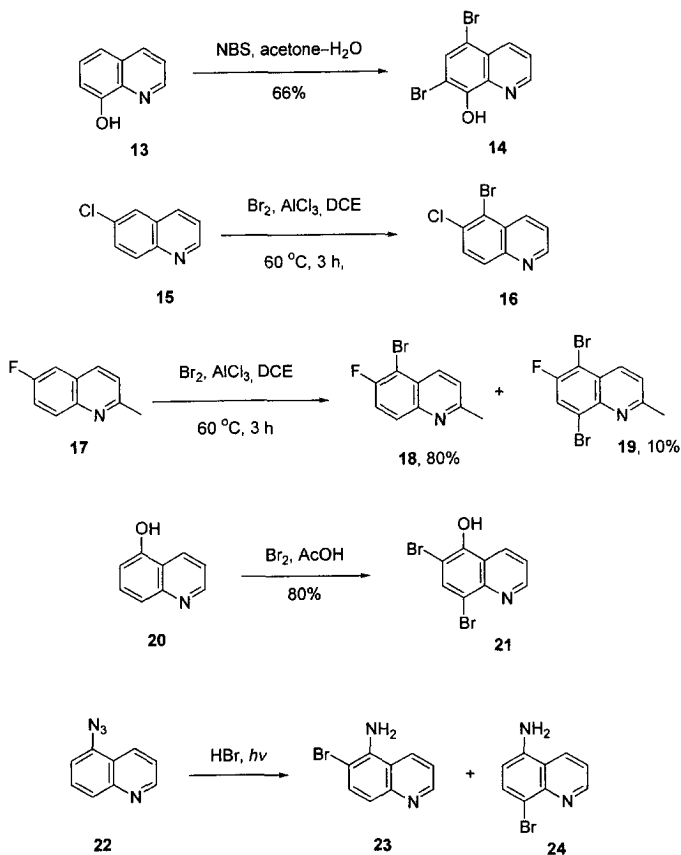
The halogenation can be carried out under more mild conditions. Sugimoto et al. (99TL7477) reported halogenation of hydroxyheterocycles using *N*-halosuccinimide and triphenylphosphine. Application of the method to 2(1*H*)-quinolone (**10**) gave 2-bromoquinoline (**11**) in 90% yield. This method has several advantages over standard halogenating reagents such as phosphorus oxyhalides. It obviates the use of caustic and expensive phosphorus oxybromide and the resulting haloheterocycles are easily isolated via  $\text{SiO}_2$  chromatography. It was also found that

in order to carry out the halogenation in good yield, 2–5 equivalents of the halogenating reagent were required. Using just one equivalent of triphenylphosphine and *N*-bromosuccinimide resulted in only 39% yield of 2-bromoquinoline (**11**).

2-Methoxy- and 4-methoxy-quinolines may behave similarly to quinolones during halogenation, in some cases they can be converted into the corresponding haloquinolines. For instance, 2- and 4-methoxyquinolines were converted to bromo compounds by Yajima and Munakata (97CL891) using a novel bromination reagent  $\text{PBr}_3$ –DMF. The reaction proceeded efficiently at 60–80 °C with no evolution of HBr which was a disadvantage with using phosphorus oxybromide by making the reaction solution strongly acidic. 2-Methoxyquinoline (**12**) furnished 2-bromoquinoline (**11**) in 78% yield, whereas 4-methoxyquinoline produced 4-bromoquinoline in 68% yield.

## B. DIRECT HALOGENATION OF QUINOLINES

Since the pyridine ring is electron-deficient, direct halogenation of quinolines rarely takes place on the pyridine motif of quinoline unless it is substituted with strong electron-donating groups. Therefore, direct halogenation of quinolines generally occurs at the benzene moiety. Commonly used halogenation reagents include NBS, NCS, and  $\text{Br}_2$  etc. For example, treatment of quinolinol **13** with NBS yielded dibromoquinolinol **14**, along with two minor quinone by-products as a consequence of oxidation by NBS (85JOC5782). Bromine, a powerful bromination agent, has found many utilities in preparing bromoquinolines. It has been known in the literature that substitution on 6-halogenated quinolines gives only 5- or 5,8-substituted compounds (64JOC329). This was applied to the bromination of 6-chloroquinoline (**15**) which gave only 5-bromo-6-chloroquinoline (**16**) (67JHC410). Similarly, 6-fluoro-2-methylquinoline (**17**) was brominated using  $\text{Br}_2$  with aluminum chloride as the catalyst and dichloroethane (DCE) as the solvent (92JHC895). The major product was the 5-bromo-6-fluoro-2-methylquinoline (**18**, 80% yield) with concurrent formation of a small amount (10%) of the 5,8-dibromo-6-fluoro-2-methylquinoline (**19**). Additionally, bromination of 5-hydroxyquinoline (**20**) normally gives both mono- and dibromides (82M531). Under basic conditions, the reaction was not regioselective, producing a mixture of mono- and dibromide, along with recovered starting material. However, under acidic conditions the reaction proceeded regioselectively, affording exclusive formation of 6,8-dibromo derivative **21** with three equivalents of bromine in acetic acid. The product is unstable but can be isolated



Scheme 2

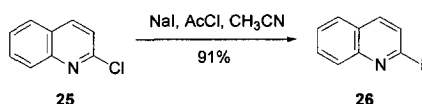
by treatment of the reaction mixture with aqueous sodium acetate (Scheme 2).

Finally, photolysis of 5-azidoquinoline (**22**) in hydrobromic acid resulted in the formation of both 6-bromo-5-aminoquinoline (**23**) and 8-bromo-5-aminoquinoline (**24**) in a 1:1 ratio (82H1043). The conversion may involve interesting intermediates such as an azirine and/or azacycloheptatetraene.

### C. S<sub>N</sub>Ar REACTION

Despite being activated by the nitrogen atom, 2-chloroquinoline (**25**) is still a poor substrate for the Stille cross-coupling reactions, though yields are usually improved under Negishi conditions. For instance, the coupling of

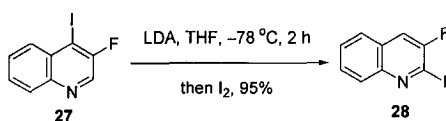
2-chloroquinoline (**25**) and 2-trimethylstannyl-6-methylpyridine under standard palladium(0)- or nickel(0)-catalyzed conditions (82ACR340, 86AGE508) was found to give poor overall yields for the desired coupled product. Thus, via the  $S_NAr$  displacement mechanism, 2-chloroquinoline (**25**) was converted to the more reactive iodo-derivative **26** in excellent yield using sodium iodide in acetyl chloride (2000T3575). The thus produced 2-iodoquinoline (**26**) was coupled efficiently with an array of stannanes to give the biaryl products in good yields (see Section IV.C). Likewise, 2-chloro-6-methoxyquinoline was converted into 2-iodo-6-methoxyquinoline in 98% yield (Scheme 3).



Scheme 3

#### D. HALOGEN-DANCE REACTION

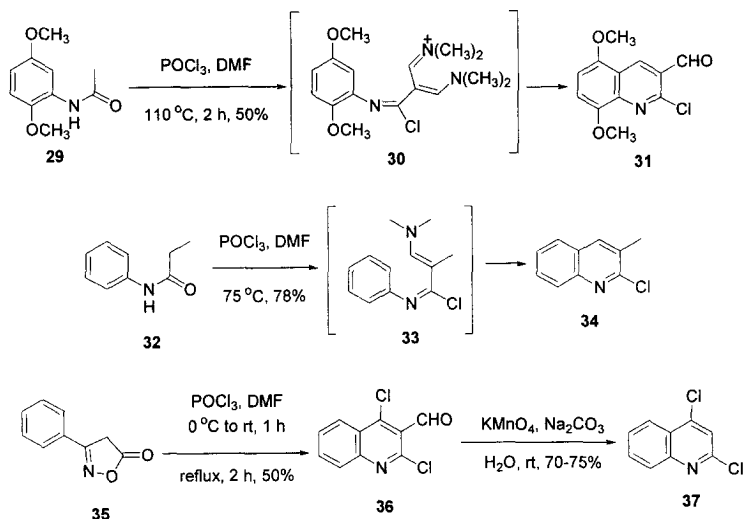
The halogen-dance reaction is a good tactic for moving the halogen substituent around the pyridine ring of quinolines. Quéguiner and coworkers (98TL6465) reported the first halogen-dance reaction in the quinoline series. Thus, treatment of the iodoquinoline **27** with LDA under the standard conditions followed by quenching with iodine led to the corresponding 3-fluoro-iodoquinoline (**28**) in 90% yield. The mechanism of halogen-dance is proposed to involve an intermolecular crossover deprotonation directed by the fluorine atom (Scheme 4).



Scheme 4

#### E. VILSMEIER-HAACK REACTION

Meth-Cohn et al. (81JCS(P1)1520) demonstrated that treatment of acetanilides with the Vilsmeier-Haack reagent (POCl<sub>3</sub>/DMF) provided chloroquinoline derivatives. As such, treatment of 2,5-dimethoxyacetanilide (**29**) with phosphorus oxychloride in DMF led to 5,8-dimethoxy-2-chloroquinoline-3-carbaldehyde (**31**) in 50% yield (93H2315). The reaction



Scheme 5

was presumed to go through a double Vilsmeier–Haack reaction via the putative intermediate **30**, which subsequently cyclized to give **31**. In the same fashion, Korodi and Cziaky (90OPP579) applied the Vilsmeier–Haack strategy developed by the Meth–Cohn group (79TL4885, 81JCS(P1)1537) in the synthesis of differently substituted 2-chloroquinolines. Thus, anilide **32** was converted to 2-chloroquinoline **34** via enamine intermediate **33** (Scheme 5).

An interesting application of the Vilsmeier–Haack reaction to 3-phenylisoxazol-5(4*H*)-one (**35**) using  $\text{POCl}_3/\text{DMF}$  resulted in 2,4-dichloroquinoline-3-carbaldehyde (**36**) through a novel rearrangement (93S623). As the 3-position of the quinoline ring is particularly unreactive, i.e. the electrophilic substitution of a formyl group at C(3) is challenging, the aforementioned method presents a useful route for the preparation of such quinolines-3-aldehydes under easily accessible substrates. Oxidation of the carbaldehyde **36** with aqueous potassium permanganate and sodium carbonate at room temperature led to the corresponding carboxylic acid, which underwent a decarboxylation process to afford 2,4-dichloroquinoline (**37**).

## F. MISCELLANEOUS SYNTHESSES OF HALOQUINOLINES

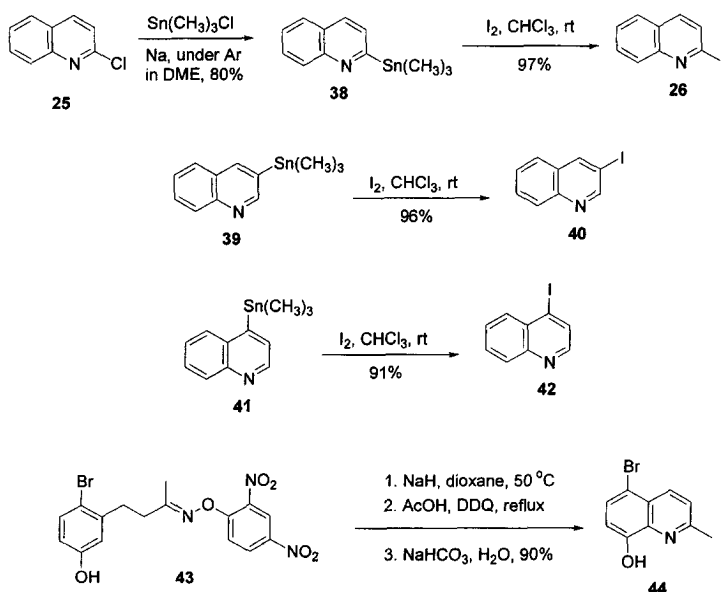
Yamamoto and Yanagi (82CPB1731) prepared iodoazines through iodo-destannylation of trimethylstannylazines. Trimethylstannyl sodium was

prepared *in situ* from chlorotrimethylstannane and metallic sodium. Subsequent treatment of 2-chloroquinoline (**25**) with trimethylstannyl sodium gave 2-trimethylstannyl quinoline (**38**). Likewise, 3- and 4-trimethylstannyl quinolines (**39**, **41**) were converted to 3- and 4-iodoquinolines (**40**, **42**) in 96 and 91% yield, respectively via iodo-destannylation. In the same fashion, 2,4-bis(trimethylstannyl)quinoline was synthesized from 4-bromo-2-chloroquinoline using two equivalents of trimethylstannyl sodium in 65% yield.

In a more “exotic” approach towards 5-haloquinolines, Uchiyama et al. (98BCJ2945) prepared 5-bromo-2-methylquinolin-8-ol (**44**) from *O*-2,4-dinitrophenyloxime **43** in one-pot. They found that the stereochemistry of the oximes did not affect the outcome of the reaction, obviating the separation of the stereochemical isomers of the oxime.

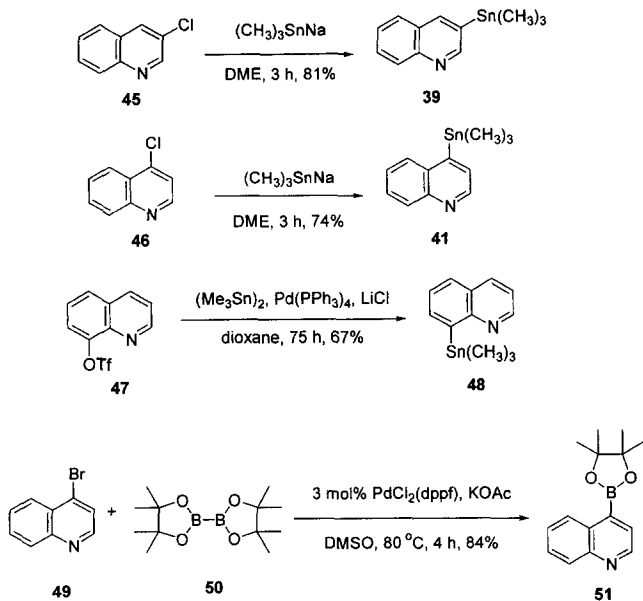
### III. Synthesis of Quinoline Nucleophiles

As depicted in Scheme 6, the  $S_NAr$  reaction between 2-chloroquinoline (**25**) and trimethylstannyl sodium led to 2-trimethylstannyl quinoline (**38**). Similarly, as shown in Scheme 7, 3-trimethylstannyl quinoline (**39**) and 4-trimethylstannyl quinoline (**41**) were prepared from 3-chloroquinoline (**45**)



Scheme 6





Scheme 7

and 4-chloroquinoline (**46**), respectively (81H1161). Furthermore, the method was extended to sodium triphenylstannane, which was treated with 2-chloroquinoline (**25**) to afford 2-triphenylstannyl quinoline in 96% yield under irradiation (92JOC5720).

Stille and coworker (87JA5478) demonstrated that palladium-catalyzed reaction between hexaalkylditin and aryl triflates led to aryl trialkylstannanes. This method has proven to be applicable to both aryl triflates and aryl halides. For example, the Stille coupling between quinolinyl-8-triflate (**47**) and hexamethylditin offered 8-trimethylstannyl quinoline (**48**) in 67% yield along with a small amount of the homocoupling product.

The Miyaura coupling reaction involving the pinacol ester of diboron **50** offers a convenient and mild preparation of arylboronic esters. Applying the methodology to 4-bromoquinoline (**49**), the Miyaura group (95JOC7508) obtained the corresponding quinolinyl-4-arylboronic ester (**51**) in 84% yield. Electron-withdrawing groups on the nucleophiles for such reactions increase the rate of reaction and the use of  $\text{KOAc}$  is essential to accelerate the reaction as well as to prevent the formation of biaryl by-products. The transmetallation step is accelerated by the use of the base.

Furthermore, Masuda and coworkers have shown that dialkoxyhydroborane can replace diboron **50** in converting aryl halides and triflates into

arylboronates (2000JOC164). In one example, treatment of 2-methoxyquinolinyl-8-triflate with 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane in the presence of  $\text{PdCl}_2\cdot(\text{dppf})$  and  $\text{Et}_3\text{N}$  in dioxane at  $80^\circ\text{C}$  for 4 h produced 2-methoxy-8-4,5,5-tetramethyl-[1,3,2]dioxaborolyquinoline in 63% yield.

## IV. Cross-coupling Reactions with Organometallic Reagents

Among the cross-coupling reactions with organometallic reagents that involve a quinoline fragment, the Suzuki and Stille coupling reactions are more prevalent, whereas there have been limited precedents for the Negishi and Hiyama reactions. Although the Stille coupling reaction is more general and the reaction conditions are neutral, it is not recommended as the first choice simply because of the toxicity of stannanes. If all equal, the Suzuki coupling reaction should be considered first while keeping in mind that the reaction needs a base (though weak bases such as  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ , and  $\text{K}_3\text{PO}_4$  are acceptable) to proceed.

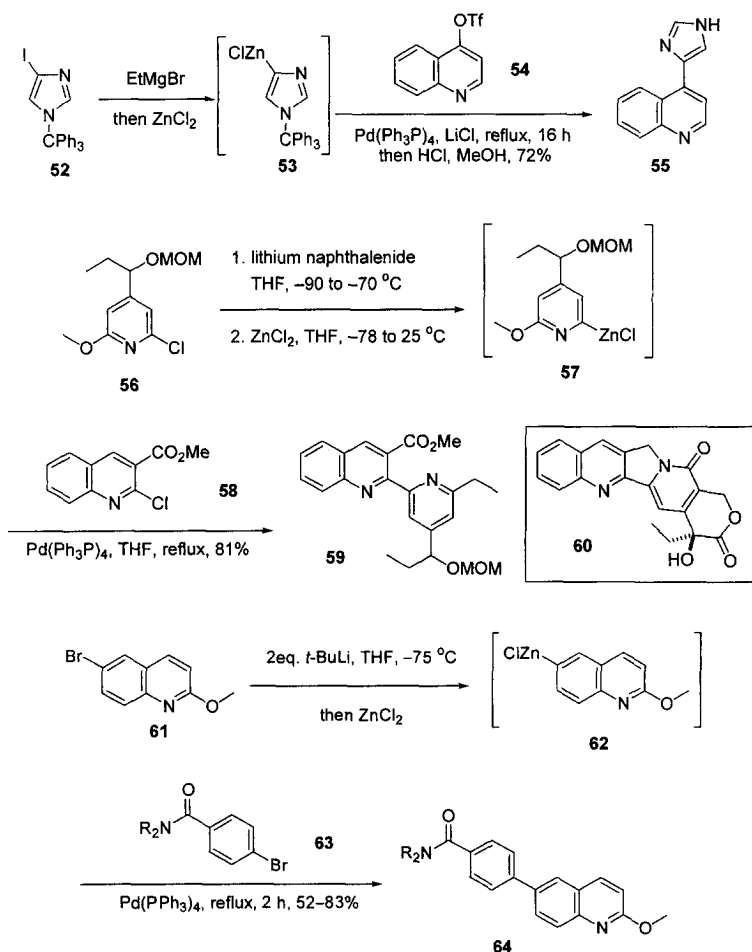
### A. NEGISHI COUPLING

In the literature, the quinolinyl motif has been used in the Negishi coupling reactions as both electrophilic and nucleophilic coupling partners. Imidazol-4-ylzinc reagent **53** was easily generated *in situ* by treating 1-trityl-4-iodoimidazole (**52**) with ethyl Grignard reagent followed by the addition of  $\text{ZnCl}_2$ . The Negishi reaction of **53** with quinolinyl-4-triflate (**54**) in the presence of  $\text{LiCl}$  led to quinolinylimidazole **55** in 72% yield after acidic removal of the trityl protection (98S829). The Negishi reaction of **53** and quinolinyl-4-bromide also gave quinolinylimidazole **55** in 74% yield. Furthermore, the authors found that the protection of the iodoimidazole could be avoided if two equivalents of  $\text{ZnCl}_2$  were employed. In another note, the coupling of quinolinyl-4-triflate (**54**) and quinolinyl-4-bromide with imidazolylstannane also provided adduct **55**, albeit in a slightly lower yield.

In their formal total synthesis of camptothecin (**60**), Murata et al. employed a Negishi reaction to establish the A, B and D ring linkage (97SL298). The halogen-metal exchange of 2-chloropyridine **56** was achieved using lithium naphthalenide complex, which was superior to *n*-BuLi because nucleophilic addition to the substrate was avoided. Transmetalation of the resulting lithiopyridine with  $\text{ZnCl}_2$  generated pyridylzinc reagent **57**, which was then coupled with methyl 2-chloro-3-quinolinecarboxylate

(58) to provide hetero biaryl 59, an important intermediate for camptothecin (60) synthesis.

Quinolinylnyl motif has been used as the nucleophilic coupling partner in the Negishi coupling reaction. Baston et al. prepared quinolinylnylzinc chloride 62 *in situ* from 6-bromo-2-methoxyquinoline (61) via halogen-metal exchange using two equivalents of *t*-butyllithium followed by quenching with  $\text{ZnCl}_2$  2000EJMC931. The subsequent Negishi coupling reaction of 62 with various 4-bromobenzamides (63) resulted in 6-aryl-substituted 2-methoxyquinolines 64 in 53–82% yield. The R group in Scheme 8 was isopropyl,



Scheme 8

isobutyl and cyclohexyl, respectively and 5-arylquinolines **64** were utilized to synthesize potent inhibitors of steroid  $5\alpha$  reductases types 1 and 2.

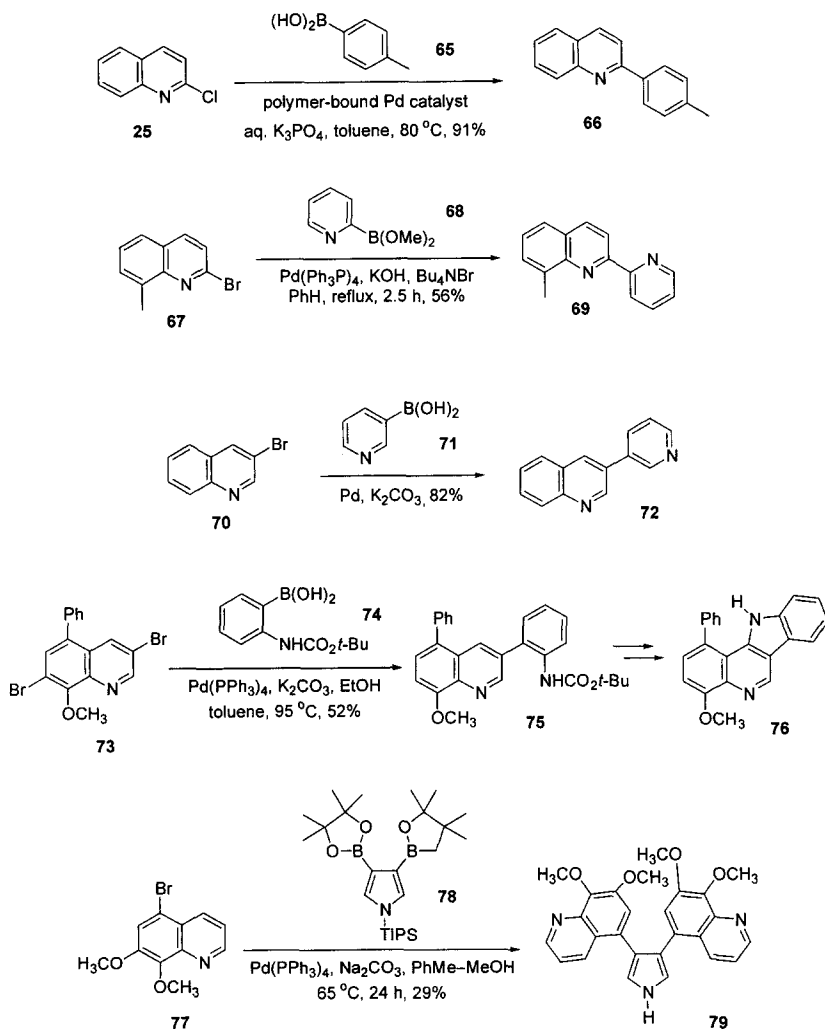
## B. SUZUKI COUPLING

Suzuki coupling entails the reactions between aryl and vinyl halides or triflates and aryl or vinyl boron compounds such as boronic acids, boronic esters, or boranes. An extremely versatile carbon-carbon forming reaction, the Suzuki reaction is useful for the preparation of unsymmetrical, bulky biaryls. The reaction requires a base. The negatively charged base coordinates to the boron atom thus increasing its nucleophilicity and promoting the transfer of the organic group on boron to the neighboring positive center on palladium. Quinoline motif can be installed from both quinolinyl halides and quinolinyl boranes in the Suzuki coupling reaction.

In the Suzuki coupling, quinolinyl halides as the electrophiles are more prevalent because they are readily available. Homogeneous catalysts present a problem of separating the catalysts from the reaction mixture. This shortcoming can be overcome by using polymer-bound palladium catalysts. Further advantages of such a catalyst are the prevention of the contamination of the products by the phosphine ligand and clean and simple work-ups. Fenger and Le Drian investigated different polymer-supported palladium catalysts as an alternative to tetrakis(triphenylphosphine)palladium catalyst in the Suzuki coupling reaction of phenylboronic acids such as **65** with 4-bromopyridine (98TL4287). Inada and Miyaura (2000T8661) have extended the method to 2-chloroquinoline (**25**). Therefore, the coupling between **25** and phenylboronic acid **65** led to 2-tolylquinoline (**66**) in 91% yield. The catalyst was recovered with ease and used in further coupling reactions. Not surprisingly, the couplings of phenylboronic acids with electron-rich chloroarenes were ineffective due to their slow oxidative addition to the palladium(0) complex.

The aforementioned reaction is an example where even quinolinyl chloride is a good substrate for the oxidative addition to palladium(0) if the chlorine atom is at the activated position ( $\alpha$  or  $\delta$ ).

Under the phase-transfer catalysis conditions, 2-bromo-8-methylquinoline (**67**) was coupled with 2-pyridylboronic ester **68** to furnish 2-(2-pyridyl)-8-methylquinoline (**69**) in 56% yield (91JOC6787). At this point, it is opportune to mention that the simple 2-pyridylborane, in contrast to 3- and (4-pyridyl)boranes, is considered an unsuitable Suzuki coupling partner because it forms an unusually stable cyclic dimer resembling a dihydroanthracene. In this case, the obstacle was circumvented by using 2-pyridylboronic ester in place of 2-pyridylborane (Scheme 9).



Scheme 9

3-Bromoquinolines behave in the Suzuki reaction similarly to simple carbocyclic aryl bromides and the reaction is straightforward. Examples include 3-(3-pyridyl)quinoline (**72**) from 3-bromoquinoline (**70**) and 3-pyridylboronic acid (**71**) (91JOC6787); and 3-phenyl-quinoline **75** from substituted 3,7-dibromoquinoline **73** and (2-pivaloylamino-5-phenylphenyl)boronic acid **74** (95SC4011). Notice that the combination of potassium carbonate and ethanol resulted in debromination at the C(7) position (but the

combination of sodium carbonate and methanol left the C(7) bromide intact). It was speculated that the debromination arose from a second palladium insertion, followed by hydrolysis of the intermediate. Further manipulations of biaryl **75** delivered an interesting 11*H*-indolo[3,2-*c*]quinoline **76**. The result is particularly interesting since the cyclization of the azide is regioselective which is not usually the case in the pyridine series (51JA2626).

In one case, an unpurified sample of pyrrolyl-bisboronic ester **78**, synthesized using conditions described by Masuda and coworkers (2000JOC164), was readily engaged in a Suzuki cross-coupling reaction (95JOC7508) with 5-bromoquinoline **77**, giving the desilylated product **79** in 29% overall yield (2002JCS(P1)1320).

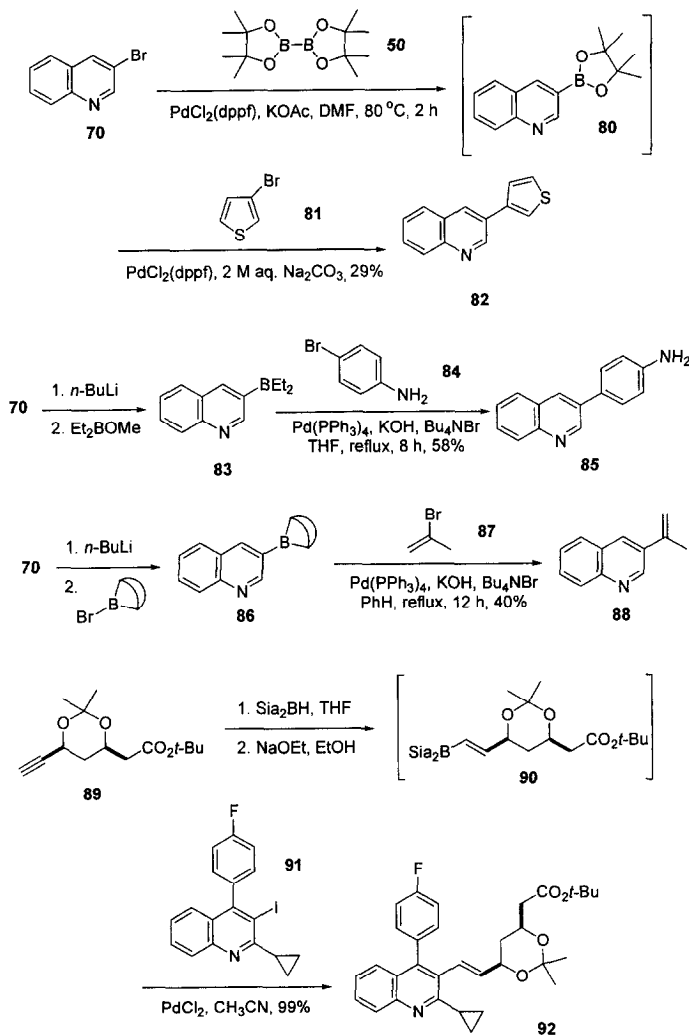
Now, we move our attention to quinolinylboron reagent as the nucleophilic coupling partners in the Suzuki coupling. In this case, quinolinylboranes are generally prepared *in situ* from the corresponding quinolinyl halides by taking advantage of the Miyaura reaction. Analogous to what we depicted in Scheme 7, 3-bromoquinoline (**70**) was transformed to quinolinyl-4-arylboronic ester (**80**) using the pinacol ester of diboron (**50**). Subsequent cross-coupling of **80** with 3-bromothiophene (**81**) then provided 3-(3-thienyl)quinoline (**82**) in 29% yield (97TL3841) (Scheme 10).

3-Dialkylquinolinyl boranes **83** and **86** were prepared from halogen/metal exchange of 3-bromoquinoline (**70**) with *n*-BuLi followed by quenching with Et<sub>2</sub>BOMe and Br-9-BBN, respectively. They are then coupled with bromides **84** and **87** to give 3-substituted quinoline derivatives **85** and **88**, respectively (85H2375).

Hiyama's group carried out a Suzuki reaction as part of their synthesis of synthetic analogues of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (93TL8267). Hydroboration of terminal alkyne **89** with disiamylborane gave vinylborane **90**, which was used *in situ* to couple with 3-iodoquinoline **91** to produce adduct **92** in 99% yield. It should be noted that although aryl iodide **91** is sterically congested, nevertheless a high yield resulted from the coupling reaction.

### C. STILLE COUPLING

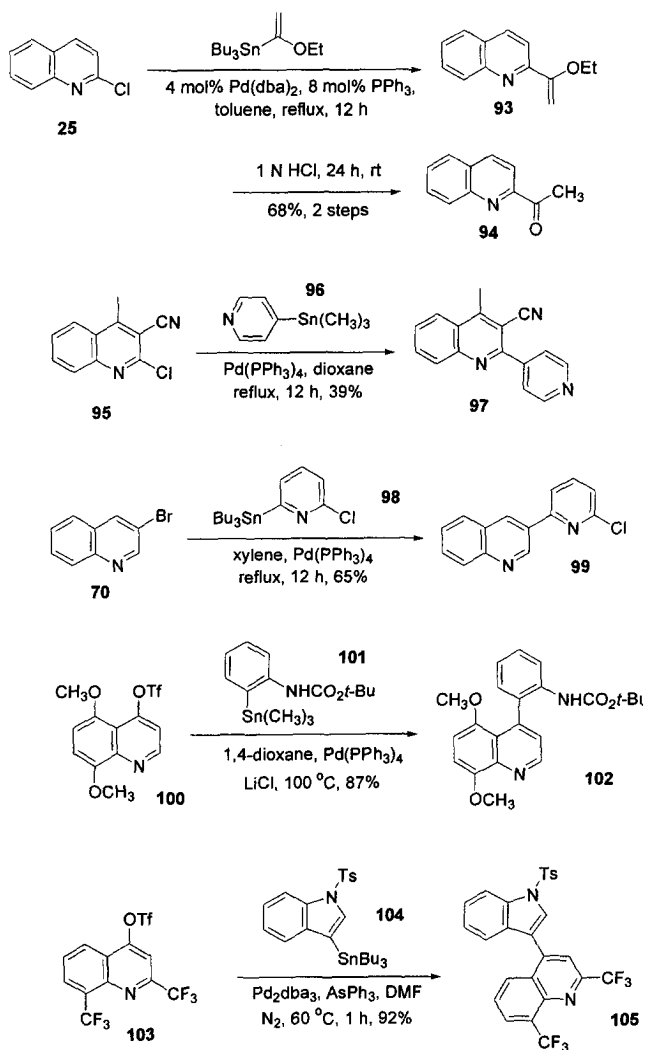
Advantages of the Stille reaction include neutral conditions under which the reaction takes place, often with full retention of stereochemistry, and compatibility with nearly all functional groups thus eliminating additional steps required for protection and deprotection. Conversely, a highly undesirable drawback is the use of toxic tin compounds and the ensuing difficult removal of these from the reaction mixture.



Scheme 10

Quinolynyl halides as the electrophiles are also more prevalent in the Stille coupling reactions. As we have learned from previous examples in Section II.C, the Stille coupling of 2- and 4-chloroquinoline is more sluggish than the corresponding Negishi reaction. However, employing a combination of  $\text{Pd}(\text{dba})_2/\text{PPh}_4$  in a 1 : 2 ratio, 2-chloroquinoline (**25**) was successfully coupled with 1-ethoxy-2-tributylstannylethene to produce adduct **93**, which was converted to 2-acetylquinoline **94** by treatment with acid (2001T2507).

Using such a tactic, all the acetyl quinoline isomers were synthesized. In the same fashion, 2-chloro-3-cyano-4-methylquinoline (**95**) was coupled with 4-trimethylstannylpyridine (**96**) under the standard Stille coupling conditions to assemble 2-(4-pyridyl)quinoline **97** in 39% yield (96LA115). With regard to 3-bromoquinoline (**70**), its coupling with 4-tributylstannyl-6-chloropyridine (**98**) was straightforward, giving rise to 3-(2-pyridyl)quinoline **99** in 65% yield (2000OL803) (Scheme 11).



Scheme 11

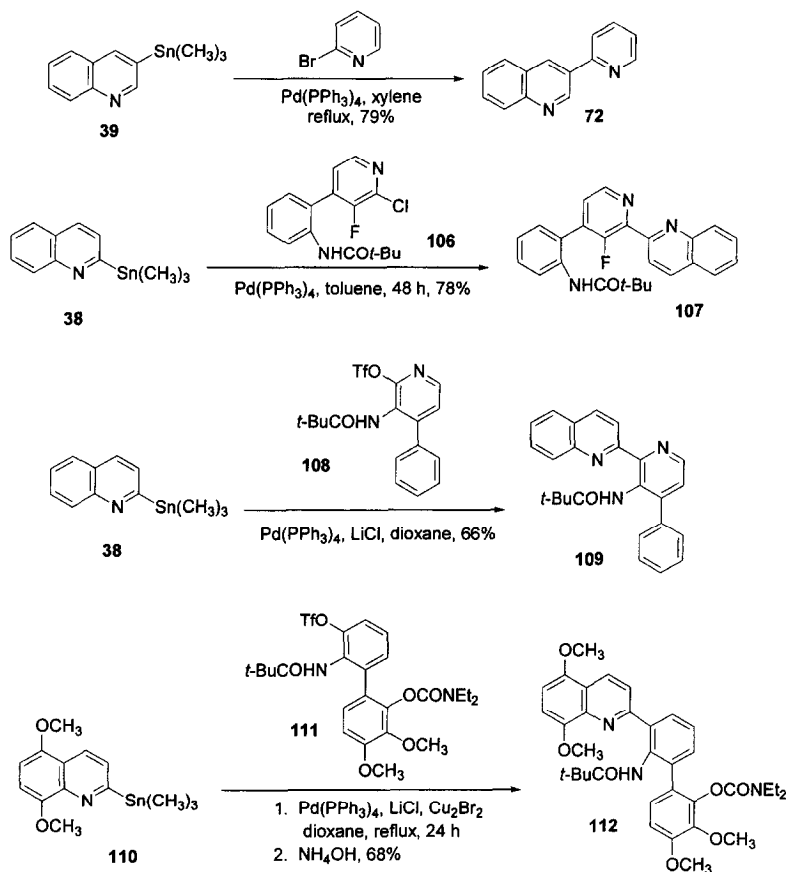


The Stille coupling of an aryl triflate normally calls for the addition of at least one equivalent of LiCl. Presumably, the transmetallation is facilitated by replacing triflate with  $\text{Cl}^-$  at the palladium intermediate generated from oxidative addition. As Stille demonstrated in 1988, 4-quinolinyl triflate **100** was coupled with phenylstannane **101** in the presence of  $\text{Pd}(\text{Ph}_3\text{P})_4$  and LiCl in refluxing 1,4-dioxane to furnish biaryl **102**, which was used as an intermediate for the first total synthesis of antibiotic amphimedine (88JA4051).

Interestingly, 4-quinolinyl triflate **103** underwent the Stille coupling smoothly with 3-tributylstannylindole **104** to deliver indolylquinoline **105** in 92% yield in the presence of  $\text{Pd}_2(\text{dba})_3\text{-AsPh}_3$  *in the absence of LiCl* (94TL2405). It is possible that this transmetallation is facilitated by the softer ligand  $\text{AsPh}_3$ .

Quinolinylstannanes serve as the nucleophilic coupling partners in the Stille coupling. As illustrated in Scheme 12, the Stille coupling of 3-trimethylstannyl quinoline **39** with 2-bromopyridine afforded 3-(2-pyridyl)quinoline (**72**) in 79% yield (86S564). Analogously, the Stille coupling of 2-trimethylstannyl quinoline (**38**) with 2-chloropyridine **106** resulted in 3-substituted quinoline **107** in 78% yield (93TL7919). In a model study (92T4123), 2-[2-(4-phenyl-3-amino)pyridyl]quinoline (**109**) was derived from the Stille coupling of 2-trimethylstannyl quinoline **38** and pyridyl triflate **108**. As an extension of the aforementioned method, decorated 2-trimethylstannyl quinoline **110** was coupled with a more intricate pyridyl triflate **111** *in the presence of LiCl* to assemble adduct **112** in 68% yield (93TL7919). Addition of  $\text{Cu}_2\text{Br}_2$  is supposed to promote the rate of transmetallation. 2-Aryl-quinoline **112** was an advanced intermediate for the total syntheses of Streptonigrin (87JMC1918) and Lavendamycin (81TL4594, 82JAN261), which have been shown to possess antitumor and antiviral activities (87JMC1918).

The powerful utility of the Stille coupling reaction is showcased by the synthesis of 4-substituted 6-nitroquipazine analogs (e.g. **116**) which are reported to have high affinities to serotonin transporter (2002BMC811). As delineated in Scheme 13, 2,4-dibromo-6-nitroquinoline (**113**) underwent a  $\text{S}_{\text{N}}\text{Ar}$  displacement by 1-piperazinecarbaldehyde to give *N*-formyl-4-bromo-6-nitroquipazine (**114**). With bromide **114** in hand, it was transformed to *N*-formyl-4-tributylstannyl-6-nitroquipazine (**115**), which was further converted by iodo-destannylation and the resulting iodide was then available for additional palladium-catalyzed reactions. Moreover, bromide **114** was utilized as the nucleophile to couple with an array of stannanes to functionalize the core structure as exemplified by **116**. An operational note is worth mentioning here for transformation **114**  $\rightarrow$  **115** via the palladium-catalyzed ditin chemistry. Tributyltin halide, the toxic by-product of the Stille coupling reaction, was removed by first quenching of the reaction



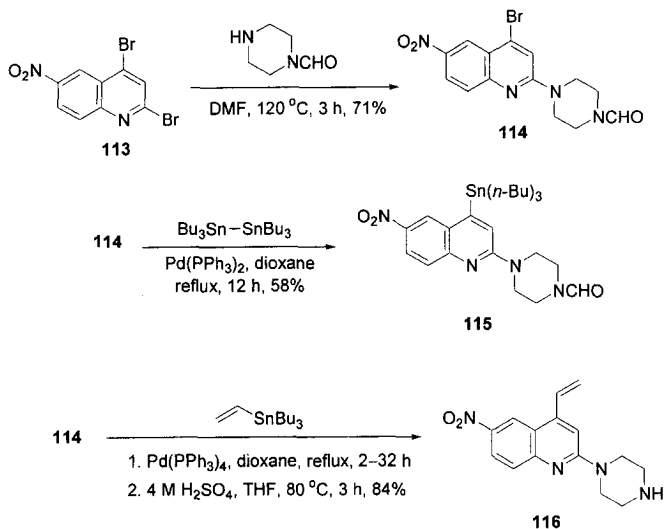
Scheme 12

mixture with the addition of 10% aqueous KF. After being stirred for 3 h, the insoluble products, palladium metal and white tributyltin polymer, were removed via filtration through Celite. Such treatment of the reaction mixture alleviated the trouble of dealing with the toxic tin by-product.

In 2002, Nikolaides et al. reported the coupling of quinolinyl-8-triflate with  $\text{Et}_4\text{Sn}$  to synthesize 8-ethylquinoline in 74% yield (2002SC2027).

## D. HIYAMA COUPLING

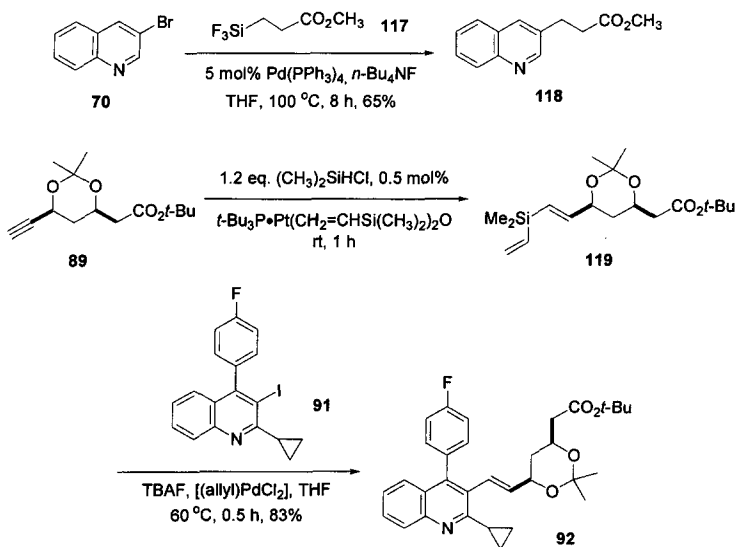
In comparison to the transmetalation of organometallic reagents including Grignard reagents, organozinc reagents and organostannanes,



Scheme 13

transmetallation of the organosilicon reagents does not occur under normal palladium-catalyzed cross-coupling conditions. The C–Si bond is much less polarized, possessing more covalent bond properties than aforementioned organometallic reagents. However, a C–Si bond can be activated by a nucleophile such as F<sup>–</sup> or HO<sup>–</sup> through formation of a pentacoordinated silicate, which weakens the C–Si bond by enhancing the polarization. As a result, the transmetallation becomes more facile and the cross-coupling proceeds readily. One of the advantages of the Hiyama coupling is that organosilicon reagents are innocuous. Another advantage is better tolerance of functional groups in comparison to other strong nucleophilic organometallic reagents. The combination of these two characteristics makes the Hiyama coupling an attractive alternative to other palladium-catalyzed cross-couplings. As a result, the Hiyama coupling reaction is sometimes called Silicon–Stille coupling. One case that involves the quinolinyl fragment is depicted in Scheme 14. Quinolinyl-3-bromide (**70**) was coupled with functionalized alkyltrifluorosilane **117** to produce adduct **118** (94TL6507) in the presence of tetrabutylammonium fluoride and catalytic Pd(PPh<sub>3</sub>)<sub>4</sub>. The Hiyama coupling reaction took place on an sp<sup>3</sup> carbon-center of the nucleophile.

In Scheme 10, HMG-CoA reductase inhibitor **92** was synthesized via a Suzuki coupling approach. Hiyama's group also carried out a Hiyama coupling to make the same compound (93TL8263). Vinylsilane **119** was prepared by platinum-catalyzed reaction from terminal alkyne **89**.



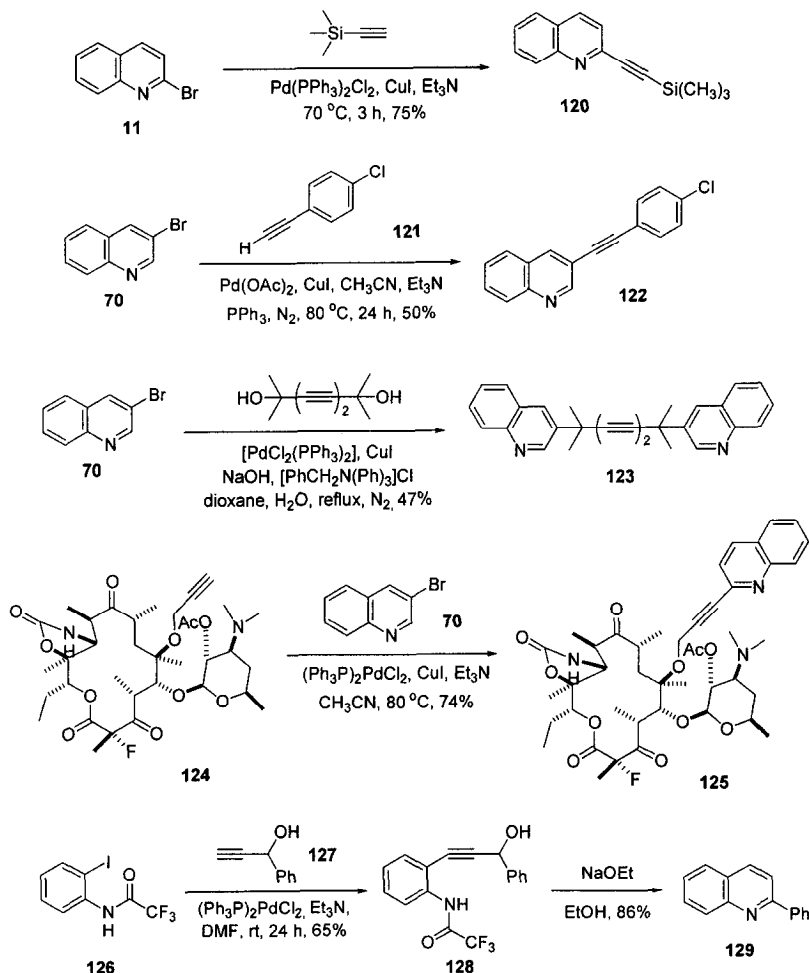
Scheme 14

Palladium-catalyzed cross-coupling between vinylsilane **119** and 3-iodoquinoline **91** then assembled **92** in 83% yield.

## V. Sonogashira Reaction

Sonogashira reaction represents a palladium-catalyzed coupling between a nucleophile (e.g. aryl- and vinyl halides) and a terminal alkyne in the presence of an aliphatic amine and catalytic palladium and CuI or CuBr. A simple example of the Sonogashira reaction involving quinoline is shown in Scheme 15. Installation of 2-trimethylsilyl ethynylquinoline (**120**, (83S312) was achieved from 2-bromoquinoline (**11**) under the standard Sonogashira reaction conditions [ $\text{PdCl}_2(\text{PPh}_3)_2$ , CuI,  $\text{Et}_3\text{N}$ ]. Under these conditions, 2-chloroquinoline (**25**) gave 87% yield at  $80 ^\circ\text{C}$  for 4 h; however, 4-chloroquinoline gave 85% recovered starting material even after  $80 ^\circ\text{C}$  for 22 h, echoing the phenomenon observed in transformation **113**  $\rightarrow$  **114**, where we saw less reactivity for halides on the C(4) position compared to the C(2) position in both  $\text{S}_\text{N}\text{Ar}$  displacement and palladium-mediated reactions.

3-Bromoquinoline (**70**), behaving similarly to a simple carbocyclic aryl bromide, was coupled with phenylethyne **121** to provide disubstituted ethyne **122** in 50% yield (2001JCS(P1)978).



Scheme 15

Although Sonogashira reaction requires terminal alkynes, 2,7-dimethylocta-3,5-diyne-2,7-diol can be readily unmasked in the presence of base. As seen in Scheme 15, diacetylene **123** was obtained from the reaction of 3-bromoquinoline (**70**) and 2,7-dimethylocta-3,5-diyne-2,7-diol in the presence of  $\text{NaOH}$ , benzyltrimethylammonium chloride as a phase-transfer catalyst, and palladium(II) and copper(I) catalysts (99HCA138). In addition, by taking advantage of the terminal alkyne on **124** as the anchor, the Sonogashira reaction attached the quinoline fragment to give 2-fluoro-6-*O*-propargyl-11,12-carbamate ketolide derivative of erythromycin, **125** (2000OL2951).

The palladium-catalyzed reaction of *o*-iodoanilides with terminal acetylenic carbinols provides a facile route to the synthesis of quinolines using readily available starting materials (93TL1625). When *o*-iodoanilide **126** was stirred with acetylenic carbinol **127** in the presence of bis-triphenyl phosphine palladium(II) chloride in triethylamine at room temperature for 24 h, the substituted alkynol **128** was obtained in 65% yield. On cyclization of **128** with sodium ethoxide in ethanol, 2-substituted quinoline **129** was obtained in excellent yield.

## VI. Heck Reaction

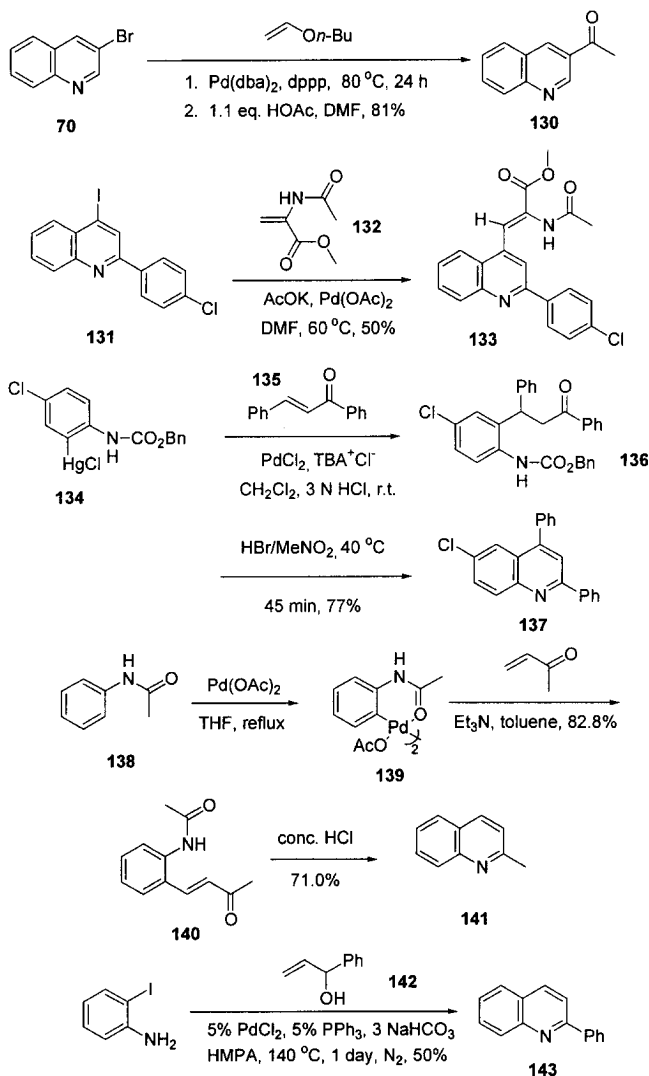
Heck reaction, palladium-catalyzed cross-coupling reactions between organohalides or triflates with olefins (72JOC2320), can take place inter- or intra-molecularly. It is a powerful carbon-carbon bond forming reaction for the preparation of alkenyl- and aryl-substituted alkenes in which only a catalytic amount of a palladium(0) complex is required.

### A. INTERMOLECULAR HECK REACTION

Legros et al. (2001T2507) carried out the synthesis of acetylquinolines (e.g. **130**) via Heck reaction of 3-bromoquinoline (**70**) and *n*-butyl vinyl ether (Scheme 16) employing either Pd(dba)<sub>2</sub> or Pd(OAc)<sub>2</sub> as the catalyst. In each case it was found that the Heck reaction for this synthesis gave better overall yields than using the Stille reaction (see Section IV.C). Another advantageous point in favor of the Heck is that it avoids the use of toxic stannane.

Due to their successful synthesis of 2-(4'-chlorophenyl)-4-iodoquinoline from the corresponding precursor acetylene, Arcadi et al. (99T13233) developed a one-step synthesis of 2,4-disubstituted quinolines via palladium-catalyzed coupling reactions. An example is the Heck reaction of 4-iodoquinoline (**131**) with  $\alpha$ -acetamidoacrylate (**132**). This one-pot synthesis yielded adduct **133** in 50% overall yield after purification via flash chromatography.

Cacchi and Palmieri (83T3373) investigated a new entry into the quinoline skeleton by palladium-catalyzed Michael-type reactions. They found that phenyl mercurial **134** was a useful intermediate for the synthesis of quinoline derivatives, and that by selecting the reaction conditions the oxidation level of the heterocyclic ring in the quinoline skeleton can be varied. On such example is shown in Scheme 16. PdCl<sub>2</sub>-catalyzed coupling between organomercurial reagent **134** and enone **135** delivered adduct **136** which was subsequently cyclized to quinoline **137** under acidic conditions.



Scheme 16

This reaction is not a *bona fide* Heck reaction *per se* for two reasons: (a) the starting material underwent a Hg–Pd transmetalation first rather than the oxidative addition of an aryl halide or triflate to palladium(0); (b) instead of undergoing an elimination step to give an enone, transformation **134** → **136** terminated the catalytic cycle with a reduction to afford a saturated alkyl ketone. Another case of Heck-like reaction is depicted in reaction **139** → **140**

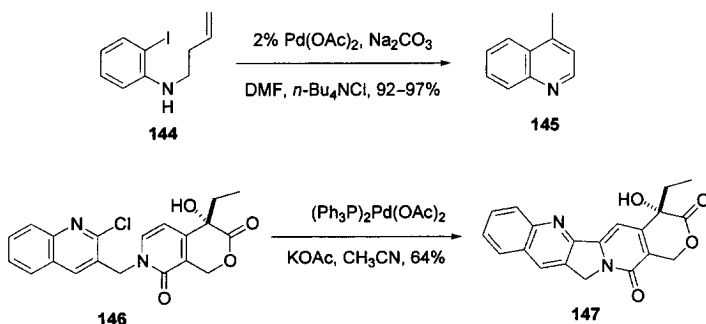
(79TL2403). Thus, *ortho*-cyclopalladation of acetanilide **138** gave organo-palladium reagent **139**. The *ortho*-vinylation of **139** afforded enone **140**, which was then cyclized to quinoline **141** under acidic conditions. Notice this reaction requires stoichiometric amounts of  $\text{Pd}(\text{OAc})_2$ .

Larock and Kuo (91TL569) investigated the palladium-catalyzed coupling of allylic alcohols and *o*-iodoaniline which provided a convenient, one-step synthesis of quinolines as represented by the reaction between *o*-iodoaniline and alkenol **142** to give quinoline **143**. The optimal conditions for this reaction were found to be 5 mol%  $\text{PdCl}_2$ , 5 mol%  $\text{PPh}_3$ , three equivalents  $\text{NaHCO}_3$ , 1.5 equivalents alkenol and 10 ml of HMPA per mmol of *o*-iodoaniline at  $140^\circ\text{C}$  for 1 day under  $\text{N}_2$ . The reaction was found to be fairly versatile and the use of a range of allylic alcohols can be utilized although the quinoline could not be isolated easily from using allylic alcohol itself.

## B. INTRAMOLECULAR HECK REACTION

Employing Jefferey's 'ligandless' conditions, Larock and Babu (87TL5291) synthesized quinolines and other nitrogen-containing heterocycles via the intramolecular Heck reaction strategy as exemplified by reaction **144**  $\rightarrow$  **145**. This reaction is similar to the Mori-Ban indole synthesis with one additional  $\text{CH}_2$  at the olefin moiety.

In a six-step synthesis of (*S*)-camptothecin (2001OL4255), the final step involved a C-ring closure using the Heck reaction. As shown in Scheme 17, 2-chloroquinoline **146** was treated with 15%  $(\text{PPh}_3)_2\text{Pd}(\text{OAc})_2$  and two equivalents KOAc in  $\text{CH}_3\text{CN}$  at  $100^\circ\text{C}$ , affording (*S*)-camptothecin (**147**) in 64% yield.



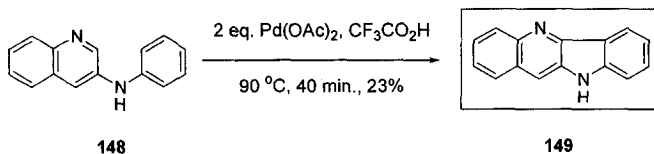
Scheme 17



## VII. Miscellaneous Reactions Mediated by Palladium

### A. OXIDATIVE CYCLIZATION

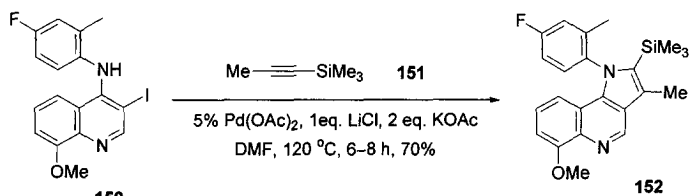
Oxidative cyclizations are generally facilitated by  $\text{Pd}(\text{OAc})_2$  in refluxing acetic acid. The role of acetic acid in such oxidative cyclization processes is to protonate the acetate ligand, making palladium(II) more electrophilic. The initial step in these oxidative cyclization reactions is electrophilic palladation of the aromatic ring. In organic synthesis, oxidative cyclization offers an expeditious route to those target molecules that may not be easily accessible otherwise. In one case, quindoline (**149**), an antimalarial agent isolated from a West African plant *Cryptolepis sanguinolenta* was synthesized in two steps, a remarkably concise synthesis (97JHC1789). The precursor, 3-anilinoquinoline (**148**), was prepared by phenylation of 3-aminoquinoline with  $\text{Ph}_3\text{Bi}(\text{OAc})_2$  in the presence of metallic copper. The crucial oxidative cyclization of **148** was then effected by *two equivalents* of  $\text{Pd}(\text{OAc})_2$  in refluxing trifluoroacetic acid to furnish quindoline (**149**) (Scheme 18).



Scheme 18

### B. HETEROANNULATION

As part of their study on gastric ( $\text{H}^+/\text{K}^+$ )-ATPase inhibitors, Kang et al. developed a simple and convenient synthetic approach to 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines by means of palladium-catalyzed heteroannulation of 4-amino-3-iodoquinoline derivatives with internal alkynes (99TL4379). Scheme 19 shows an example of a reaction using 4-aryl-amino-3-iodoquinoline derivative **150** with alkyne **151** to provide 1-arylpyrrolo[3,2-*c*]quinoline **152**, illustrating the possibility of introducing diverse substituents to 1-arylpyrrolo[3,2-*c*]quinolines. In addition, a palladium-catalyzed domino hydroarylation/cyclization process was reported to form substituted quinolines (2002TL5537). Therefore, 3-arylquinolines were prepared in 56–74% yield when 3,3-diethyl-1-phenyl-1-propyne and aryl iodide were refluxed in ionic liquid, 1-butyl-3-methylimidazolium



Scheme 19

tetrafluoroborate  $[(\text{bmim})\text{BF}_4^-]$ , in the presence of  $\text{HCO}_2\text{H}$ ,  $\text{Et}_3\text{N}$  and palladium catalyst. Meanwhile, 4-arylquinolines were obtained in 9–21% yield as minor by-products.

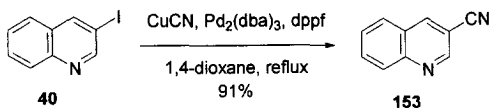
### C. CYANATION

The nitrile group is a stable and versatile functional group which can be converted into several other functionalities by relatively simple synthetic routes. Thus the addition of this group into a molecule provides a route by which it can be manipulated into a more complex compound. Sakamoto and Ohsawa (99JCS(P1)2323) investigated the cyanation of various quinolines using copper(I) cyanide as the cyano group source. In the presence of catalytic amount of  $\text{Pd}_2(\text{dba})_3$ , and  $\text{dppf}$  as ligand, 3-iodoquinoline (**40**) was cyanated to give 4-cyanoquinoline (**153**) in 91% yield. To confirm that their method was indeed catalyzed by palladium, they also ran their reactions without the palladium catalysts and found in most cases that little or none of the desired product was obtained, and mostly the starting material was recovered (Scheme 20).

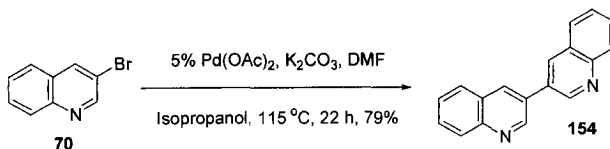
The mechanism of action of the cyanation reaction is considered to progress as follows: an oxidative addition reaction occurs between the aryl halide and a palladium(0) species to form an arylpalladium halide complex which then undergoes a ligand exchange reaction with  $\text{CuCN}$  thus transforming to an arylpalladium cyanide. Reductive elimination of the arylpalladium cyanide then gives the aryl cyanide.

### D. HOMOCOUPLING

Traditionally, the synthesis of symmetrical biaryls was routinely accomplished using the Ullmann reaction. Recently, palladium-catalyzed homocoupling of aryl halides has also been demonstrated to rival the utility of the Ullmann coupling. As illustrated in Scheme 21, using  $\text{Pd}(\text{OAc})_2$  as the



Scheme 20

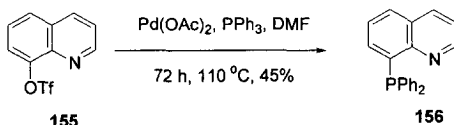


Scheme 21

catalyst,  $\text{K}_2\text{CO}_3$  as the base in isopropanol (98T13793), 3-bromoquinoline (**70**) was homocoupled to produce bis-quinoline **154** in 79% yield. Under the same reaction conditions, 2-chloroquinoline was homocoupled to give its corresponding dimer in 79% yield.

## E. PHOSPHINATION

Tertiary phosphines are an important family of ligands in transition metal-catalyzed reactions. Palladium-catalyzed phosphination with triarylphosphines to produce functionalized tertiary phosphines was carried out by Kwong et al. (2000TL10285). Using  $\text{Pd}(\text{OAc})_2$  as the catalyst,  $\text{PPh}_3$  as both the ligand and phosphinating agent, quinolinyl-8-triflate (**155**) was converted to quinolinyl-8-diphenylphosphine (**156**) in 45% yield. The method was compatible with many functional groups such as aldehyde, ketone, nitrile, ester, methoxy, and pyridyl groups. Typical reactions involving simple carbocyclic substrates only took 2–6 h; however, quinolinyl and pyridyl triflates took longer to transform to their corresponding phosphines. This was presumably due to the coordination of the chelating heteroatom to the palladium center, thus causing it to be coordinatively saturated, hence reducing its catalytic activity (Scheme 22).



Scheme 22

In summary, palladium-mediated reactions, especially cross-coupling reactions have found many applications in quinoline synthesis. It is noteworthy that due to the  $\alpha$  and  $\delta$  activation for the C(2) and C(4) positions, even 2-chloro- and 4-chloro-quinolines are viable substrates for palladium-catalyzed reactions under standard conditions. With the advent of the palladium chemistry and more commercially available organometallic substrates, more palladium-mediated quinoline syntheses are to be added to the repertoire of quinoline chemistry.

## REFERENCES

- 51JA2626 P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 2626 (1951).  
64JOC329 M. Gordon and D. E. Pearson, *J. Org. Chem.*, **29**, 329 (1964).  
67JHC410 M. Gordon, H. Hamilton, C. Adkins, J. Hay, and D. E. Pearson, *J. Heterocycl. Chem.*, **4**, 410 (1967).  
72JOC2320 R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, **37**, 2320 (1972).  
79TL2403 H. Horino and N. Inoue, *Tetrahedron Lett.*, **20**, 2403 (1979).  
79TL4885 O. Meth-Cohn, S. Rhouati, and B. Tarnowski, *Tetrahedron Lett.*, **20**, 4885 (1979).  
81H1161 Y. Yamamoto and A. Yanagi, *Heterocycles*, **16**, 1161 (1981).  
81JCS(P1)1520 O. Meth-Cohn, B. Narine, and B. Tarnowski, *J. Chem. Soc., Perkin Trans. 1*, 1520 (1981).  
81JCS(P1)1537 O. Meth-Cohn, S. Rhouati, B. Tarnowski, and A. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 1537 (1981).  
81TL4594 T. W. Doyle, D. M. Balitz, R. E. Grulich, and D. E. Nettleton, *Tetrahedron Lett.*, **22**, 4595 (1981).  
82CPB1731 Y. Yamamoto, A. Yanagi, *Chem. Pharm. Bull.*, **30**, 1731 (1982).  
82ACR340 E. Negishi, *Acc. Chem. Res.*, **15**, 340 (1982).  
82H1043 H. Sawanishi, T. Hirai, and T. Tsuchiya, *Heterocycles*, **19**, 1043 (1982).  
82JAN261 D. M. Balitz, J. A. Bush, W. T. Bradner, F. A. O'Herron, and D. E. Nettleton, *J. Antibiot.*, **25**, 261 (1982).  
82M531 Z. H. Skraup, *Monatsh. Chem.*, **3**, 531 (1982).  
83S312 T. Sakamoto, M. Shiraiwa, Y. Kondo, and H. Yamanaka, *Synthesis*, 312 (1983).  
83T3373 S. Cacchi and G. Palmieri, *Tetrahedron*, **39**, 3373 (1983).  
85H2375 M. Ishikura, I. Oda, and M. Terashima, *Heterocycles*, **23**, 2375 (1981).  
85JOC5782 D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, **50**, 5782 (1985).  
86S564 Y. Yamamoto, Y. Azuma, and H. Mitoh, *Synthesis*, 564 (1986).  
86AGE508 J. K. Stille, *Angew. Chem. Int. Ed.*, **25**, 508 (1986).  
87JA5478 A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987).  
87JMC1918 D. L. Boger, M. Yasuda, L. A. Mitscher, S. D. Drake, Paul A. Kitos, and S. C. Thompson, *J. Med. Chem.*, **30**, 1918 (1987).  
87TL5291 R. C. Larock and S. Babu, *Tetrahedron Lett.*, **28**, 5291 (1987).  
88JA4051 A. M. Echavarren and J. M. Stille, *J. Am. Chem. Soc.*, **110**, 4051 (1988).  
90OPP579 F. Korodi and Z. Cziaky, *Org. Prep. Proced. Int.*, **22**, 579 (1990).

- 91JMC1202 P. J. M. Van Galen, P. Nissen, I. Van Wijngaarden, A. P. Ijzerman, and W. Soudijn, *J. Med. Chem.*, **34**, 1202 (1991).
- 91JOC6787 K. Deshayes, R. D. Broene, I. Chao, C. B. Knobler, and F. Diederich, *J. Org. Chem.*, **56**, 6787 (1991).
- 91TL569 R. C. Larock and M.-Y. Kuo, *Tetrahedron Lett.*, **32**, 569 (1991).
- 92JHC895 P. Bouyssou, C. Le Goff, and J. Chenault, *J. Heterocycl. Chem.*, **29**, 895 (1992).
- 92JOC5720 C. C. Yammal, J. C. Podesta, and R. A. Rossi, *J. Org. Chem.*, **57**, 5720 (1992).
- 92T4123 A. Godard, J.-C. Rovera, F. Marsais, N. Ple, and G. Queguiner, *Tetrahedron*, **48**, 4123 (1992).
- 93H2315 M. M. Alonso, M. del Mar Blanco, C. Avendano, and J. C. Menendez, *Heterocycles*, **36**, 2315 (1993).
- 93S623 K. Ashok, G. Sridevi, and Y. Umadevi, *Synthesis*, 623 (1993).
- 93TL1625 N. G. Kundu, J. S. Mahanty, P. Das, and B. Das, *Tetrahedron Lett.*, **34**, 1625 (1993).
- 93TL7919 A. Godard, P. Rocca, J.-M. Fourquez, J.-C. Rovera, F. Marsais, and G. Quéguiner, *Tetrahedron Lett.*, **34**, 7919 (1993).
- 93TL8263 K. Takahashi, T. Minami, Y. Ohara, T. Hiyama, *Tetrahedron Lett.*, **34**, 8263 (1993).
- 93TL8267 N. Miyachi, Y. Yanagawa, H. Iwasaki, Y. Ohara, T. Hiyama, *Tetrahedron Lett.*, **34**, 8267 (1993).
- 94TL2405 P. G. Ciattini, E. Morera, G. Ortá, *Tetrahedron Lett.*, **35**, 2405 (1994).
- 94TL6507 H. Matsuhashi, M. Kuroboshi, Y. Hatanaka, T. T. Hiyama, *Tetrahedron Lett.*, **35**, 6507 (1994).
- 95JOC7508 T. Ishiyama, M. Murata, and N. Miyaara, *J. Org. Chem.*, **60**, 7508 (1995).
- 95SC4011 F. Trecourt, F. Mongin, M. Mallet, and G. Queguiner, *Synth. Commun.*, **25**, 4011 (1995).
- 96LA115 F. Bracher, T. Papke, and J.-Y. Legros, *Liebigs Ann. Chem.*, 115 (1996).
- 97CL891 T. Yajima and K. Munakata, *Chem. Lett.*, **8**, 891 (1997).
- 97JHC1789 P. Fan and S. Y. Ablordeppey, *J. Heterocycl. Chem.*, **34**, 1789 (1997).
- 97SL298 N. Murata, T. Sugihara, Y. Kondo, and T. Sakamoto, *Synlett*, 298 (1997).
- 97TL3841 A. Giroux, Y. Han, and P. Prasit, *Tetrahedron Lett.*, **38**, 3841 (1997).
- 98BCJ2945 K. Uchiyama, A. Ono, Y. Hayashi, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **71**, 2945 (1998).
- 98S829 M. Jetter and A. B. Reitz, *Synthesis*, 829 (1998).
- 98T13793 J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, and M. Lemaire, *Tetrahedron*, **54**, 13,793 (1998).
- 98TL4287 I. Fenger and C. Le Drian, *Tetrahedron Lett.*, **39**, 4287 (1998).
- 98TL6465 E. Arzel, P. Rocca, F. Marsais, A. Godard, and G. Queguiner, *Tetrahedron Lett.*, **39**, 6465 (1998).
- 99HCA138 A. Sarkar, S. Okada, H. Nakanishi, and H. Matsuda, *Helv. Chim. Acta*, **82**, 138 (1999).
- 99JCS(P1)2323 K. Sakamoto and K. Ohsawa, *J. Chem. Soc., Perkin Trans. 1*, 2323 (1999).
- 99T13233 A. Arcadi, F. Marinelli, and E. Rossi, *Tetrahedron*, **55**, 13,233 (1999).

- 99TL4379 S. K. Kang, S. S. Park, S. S. Kim, J.-K. Choi, and E. K. Yum, *Tetrahedron Lett.*, **40**, 4379 (1999).
- 99TL7477 O. Sugimoto, M. Mori, and K.-I. Tanji, *Tetrahedron Lett.*, **40**, 7477 (1999).
- 2000EJMC931 E. Baston, A. Paluszczak, and R. W. Hartmann, *Eur. J. Med. Chem.*, **35**, 931 (2000).
- 2000JMC3244 A. Wissner, D. M. Berger, D. H. Boschelli, M. B. Floyd, Jr., L. M. Greenberger, B. C. Gruber, B. D. Johnson, N. Mamuya, R. Nilakantan, M. F. Reich, R. Shen, H.-R. Tsou, E. Upešlacis, Y. F. Wang, B. Wu, F. Ye, N. Zhang, *J. Med. Chem.*, **43**, 3244 (2000).
- 2000JOC164 M. Murata, T. Oyama, S. Watanabe, and Y. Masuda, *J. Org. Chem.*, **65**, 164 (2000).
- 2000OL803 S. Choppin, P. Gros, Y. Fort, *Org. Lett.*, **2**, 803 (2000).
- 2000OL2951 L. T. Phan, R. F. Clark, M. Rupp, Y. S. Or, D. T. W. Chu, and D. Ma, *Org. Lett.*, **2**, 2951 (2000).
- 2000T3575 M. Kimber, P. I. Anderberg, and M. M. Harding, *Tetrahedron*, **56**, 3575 (2000).
- 2000T8661 K. Inada and N. Miyaara, *Tetrahedron*, **56**, 8661 (2000).
- 2000TL10285 F. Y. Kwong, C. W. Lai, Y. Tian, and K. S. Chan, *Tetrahedron Lett.*, **41**, 10,285 (2000).
- 2001JCS(P1)978 M. Armengol and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 978 (2001).
- 2001OL4255 D. L. Comins and J. M. Nolan, *Org. Lett.*, **3**, 4255 (2001).
- 2001T2507 J.-Y. Legros, G. Primault, and J.-C. Fiaud, *Tetrahedron*, **57**, 2507 (2001).
- 2002BMC811 B. S. Lee, S. Chu, B.-S. Lee, D. Y. Chi, Y. S. Song, and C. Jin, *Bioorg. Med. Chem. Lett.*, **12**, 811 (2002).
- 2002JCS(P1)1320 M. G. Banwell, A. M. Bray, A. J. Edwards, and D. J. Wong, *J. Chem. Soc., Perkin Trans. 1*, 1320 (2002).
- 2002SC2027 N. Nikolaidis, S. E. Bogdan, and J. S. Szalma, *Synth. Commun.*, **32**, 2027 (2002).
- 2002TL5537 S. Cacchi, G. Fabrizi, A. Goggiamani, M. Moreno-Mañas, and A. Vallribera, *Tetrahedron Lett.*, **43**, 5537 (2000).

# Pyrimidine–Pyridine Ring Interconversion

H.C. VAN DER PLAS

*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8,  
6703 HB, Wageningen, The Netherlands*

I. Introduction	31
II. Pyrimidine-to-pyridine Ring Transformation	32
A. Nucleophile-induced Transformations	33
1. Fragmentation of the Pyrimidine Ring	33
2. N/C Replacement	34
3. C–N/C–C Replacement	36
4. N–C–C/C–C–C Replacement	44
5. N–C–N/N–C–C Replacement	45
6. NCNC/NCCC Replacement	49
7. Isomerizations	49
B. Hetero Diels–Alder Cycloaddition	51
1. Intermolecular IHDA Cycloadditions Involving C–N/C–C Replacements	51
2. Intramolecular IHDA Cycloadditions Involving C–N/C–C Replacements	54
3. Intermolecular NHDA Cycloadditions Involving N–C/C–C Replacements	60
4. Intramolecular NHDA Cycloadditions Involving N–C/C–C Replacements	62
III. Pyridine-to-pyrimidine Ring Transformation	63
References	65

## I. Introduction

The study on ring transformations of heterocycles is an attractive subject of research for many years. This great interest is due to the fact that these reactions are usually easily performed and that by these ring transformations heterocycles can be synthesized which are otherwise difficult to obtain. Moreover, unravelling the course of the ring transformation has always been a challenging problem and has attracted the interest of many chemists; it requires studies on substituent and solvent effects, labeling and NMR studies, kinetic studies and quantum chemical calculations. In the course of

the last 30 years several review articles have been published dealing with these different aspects of ring transformations and discussing the various heterocyclic ring systems which can undergo these ring interconversions. Examples are the monocyclic rearrangement of five-membered heterocycles (74MI1, 77AG(E)572, 81AHC141, 82T3537, 84JHC627, 84MI1, 92AHC49), the rearrangement reactions of pyrylium salts (82MI1), the conversion of pyridines into benzenes (81T3423, 88KGS1570), the ring transformations of pyrimidines (73MI1, 74MI2, 78ACR462, 78H33, 78KGS867, 80WCH491, 84H289, 85T237, 88AHC302, 89AHC73, 94KGS1649, 95H(40)441, 02THC1).

The *meta* position of the ring nitrogens in pyrimidine makes this electron-deficient ring system very vulnerable for nucleophilic attack, especially at the positions 2, 4 and 6. The well-documented replacement of ring hydrogens by nucleophiles ( $S_NH$  substitutions) illustrates this behavior (78ACR462, 94MI1). This highly electron-deficiency of the pyrimidine ring makes this heterocyclic system also very appropriate to undergo nucleophile (base)-induced ring transformations and to react with electron-rich olefins and alkynes in cycloaddition reactions. It is the intention of the author to discuss in this review the pyrimidine-to-pyridine ring transformation as well as the pyridine-to-pyrimidine ring transformation.

The first extensive authoritative review on ring transformations was published in 1972/1973 (73MI1), and in this review only about 10 literature references were cited dealing with ring interconversions of pyrimidines and pyridines. In the present review more than 100 papers on these interconversions are mentioned, showing the general interest on this topic during the last three decades. Degenerate pyrimidine-to-pyrimidine ring transformations will not be discussed in this review, since this topic has extensively been reviewed very recently (99AHC1).

## II. Pyrimidine-to-pyridine Ring Transformation

In nucleophile-induced pyrimidine-to-pyridine rearrangements, two types of reactions can be distinguished depending on the structure of the nucleophile: (i) reactions in which the nitrogen in the pyridine ring originates from the nitrogen of the pyrimidine ring; or (ii) reactions in which the pyridine nitrogen is derived from a nitrogen-containing reagent. The nucleophile-induced rearrangement usually involves as first step the Addition of the Nucleophile to the C–N bond in the pyrimidine ring, a subsequent Ring Opening, involving a C–N bond breaking and Ring Closure. This reaction sequence is usually described as ANRORC mechanism.



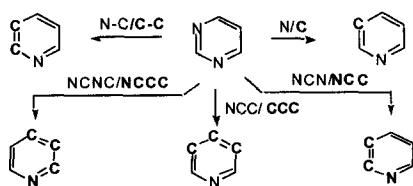
Besides nucleophile-induced transformations the Hetero Diels-Alder (HDA) cycloaddition reactions are also very suitable ways to perform the pyrimidine-to-pyridine ring transformations. They can occur either by a reaction of an electron-poor pyrimidine system with an electron-rich dienophile (inverse HDA reactions) or by reacting an electron-enriched pyrimidine with an electron-poor dienophile (normal HDA reactions) (see Section II.B).

### A. NUCLEOPHILE-INDUCED TRANSFORMATIONS

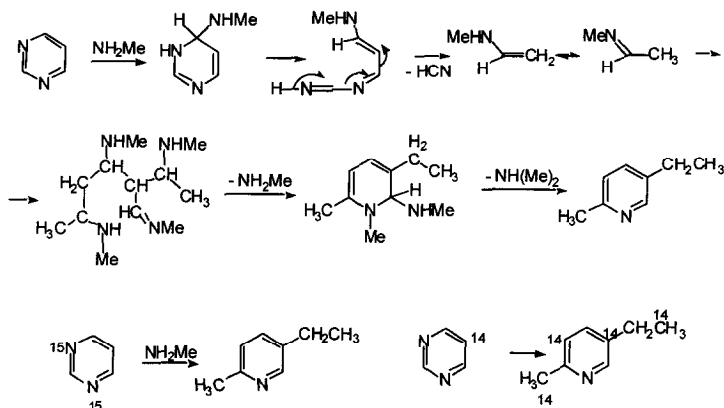
Most of the nucleophile (base)-induced pyrimidine-to-pyridine conversions can be classified as follows: (i) fragmentation of the pyrimidine ring to a two-carbon and/or four atom fragment, followed by recyclization (Section II.A.1); (ii) replacement of one ring nitrogen by one carbon atom (Section II.A.2); (iii) replacement of a C-N part of the pyrimidine ring by a C-C fragment (Section II.A.3); (iv) replacement of a N-C-C triad by a C-C-C fragment (Section II.A.4); (v) replacement of the N-C-N triad by a N-C-C fragment (Section II.A.5); and (vi) the replacement of the N-C-N-C moiety by C-C-C-N moiety (Section II.A.6) and isomerization reactions (Section II.A.7). All these replacement reactions are summarized in Scheme 1.

#### 1. Fragmentation of the Pyrimidine Ring

There are several pyrimidine-to-pyridine transformations reported, where under influence of acid, ammonia or amines, a breakdown of the pyrimidine ring takes place into two (four)-carbon fragments, which with the nitrogen of the ammonia(amine) form the building blocks for reassembling the pyridine ring. An interesting example of fragmentation of the pyrimidine ring is the low-yield formation of 5-ethyl-2-methylpyridine, being obtained on heating of pyrimidine with methylamine/water at 190 °C (71RTC1246) (Scheme 2). It is assumed that the pyrimidine ring "breaks down" to acetaldimine, that subsequently reacts with ammonia or methylamine in a



Scheme 1



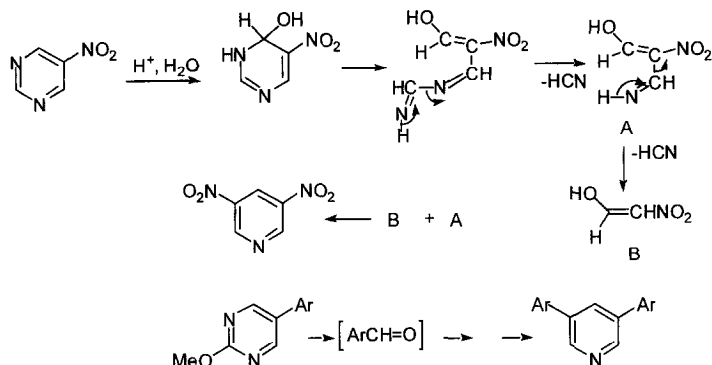
Scheme 2

repeatedly occurring aldol-condensation into 5-ethyl-2-methylpyridine. This assumption is supported by a  $^{15}\text{N}$  and  $^{14}\text{C}$  labeling study of the reaction (76RTC104). Using  $^{15}\text{N}$  labeled pyrimidine it was found that the pyridine ring is unlabeled, proving that the pyridine ring nitrogen is derived from the nitrogen of the amine. When  $[5\text{-}^{14}\text{C}]$ -pyrimidine was used as a substrate, it was observed that in 5-ethyl-2-methylpyridine both C-3 and C-5 of the pyridine ring, as well as the carbon of the methyl group on position 2 and the carbon of the methyl group in the ethyl side-chain were  $^{14}\text{C}$  labeled (Scheme 2); it clearly indicates that the C-4(6)–C-5 fragment of the pyrimidine ring is involved in the ring transformation. Additional evidence for this mechanism can be taken from the experiment that acetaldehyde indeed reacts with ammonia into 5-ethyl-2-methylpyridine (60MI1).

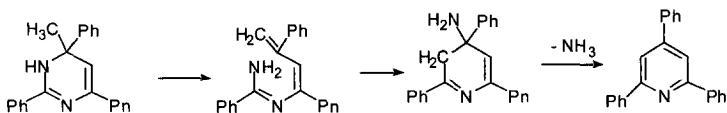
Another example, illustrating this type of ring transformation is the formation of 3,5-dinitropyridine from 5-nitropyrimidine on heating with acetic acid in water (78JHC485) (Scheme 3). The reaction has been described as a fragmentation of the pyrimidine ring in a two-carbon C-4–C-5( $\text{NO}_2$ ) moiety and a four-atom C-4–C-5( $\text{NO}_2$ )–C-6–N-1 fragment which undergo an aldol-type condensation into the pyridine ring. A somewhat similar result was found when 5-aryl-2-methoxypyrimidines are heated with ethanolic ammonia, 3,5-arylpdridines being obtained. An arylacetaldehyde was suggested as intermediate (70AJC625) (Scheme 3).

## 2. N/C Replacement

An early example of N/C replacement leading to a pyrimidine–pyridine conversion is observed on thermolysis ( $240^\circ\text{C}$ ) of 2,4,6-triphenyl-4-methyl-3,4-dihydropyrimidine. During the thermolysis ammonia evolves and in

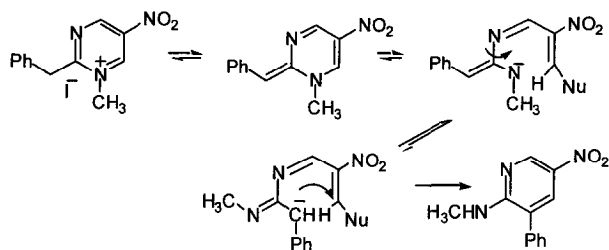


Scheme 3

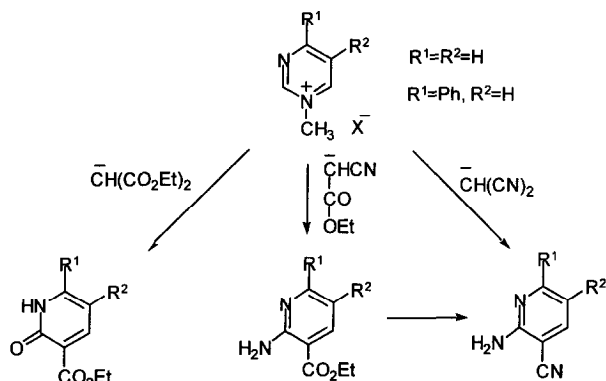


Scheme 4

53% yield 2,4,6-triphenylpyridine is obtained (79TL1241, 82JCRS113). It seems feasible to describe this rearrangement by a 1,3-hydrogen shift into an 1-amino-2-azahexatriene, followed by an electrocyclic ring closure and elimination of ammonia (Scheme 4). Several pyrimidine-to-pyridine ring transformations are achieved by the base-induced Kost-Sagitullin rearrangements. These rearrangements occur with *N*-alkylazinium salts, which are substituted by one or more electron-withdrawing groups, and having on the position adjacent to the ring nitrogen a substituent with an acidic hydrogen on carbon (e.g. methyl, benzyl, alkoxy(amino)carbonylmethyl). In these rearrangements the side-chain carbon will be incorporated in the (hetero)aromatic ring and the *N*-alkyl ring nitrogen moves outside the ring, becoming the alkylamino substituent. In these rearrangements the azine C–N bond undergoes bond breaking, resulting in an open-chain intermediate, whose recyclization leads to the formation of a (substituted amino) side-chain (Scheme 4). Examples of these rearrangements are the conversion of 2-benzyl-1,4,6-trimethylpyrimidinium salts into 4,6-dimethyl-2-methylamino-3-phenylpyridine (78TL4135), of 1-methyl-2-benzyl-5-nitro-pyrimidinium salts into 2-methylamino-5-nitro-3-phenylpyridine (00KGS698, 00CHC613) (Scheme 5) and of 1-alkyl-2-(ethoxycarbonylmethyl)pyrimidinium iodides into 2-(alkylamino)nicotinic acids (00H419, 99CHC1375). All these reactions follow an ANRORC-type mechanism. After deprotonation into the  $\beta$ -enamine, addition of the base occurs at



Scheme 5

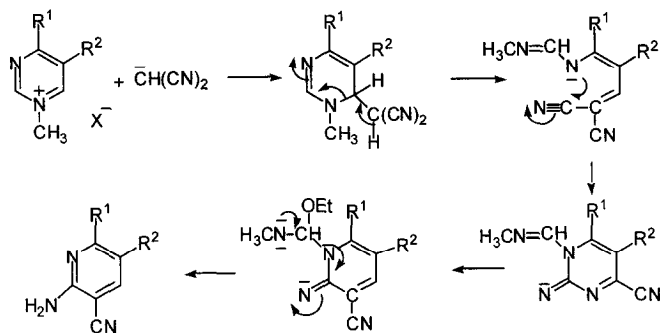


Scheme 6

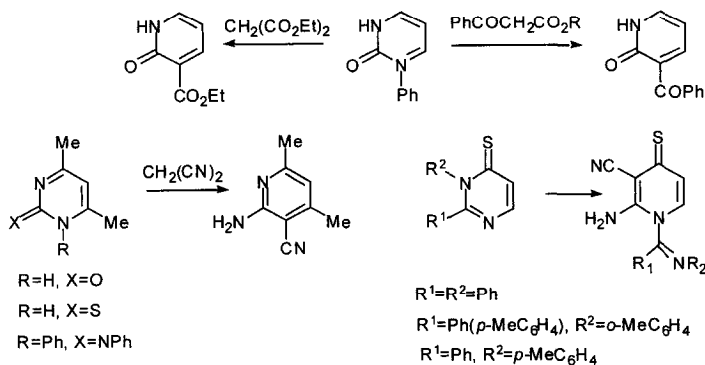
position 6, followed by bond breaking between N-1 and C-6 and ring closure with C-C bond formation (Scheme 5).

### 3. C-N/C-C Replacement

CN/CC replacement have been found in reactions of pyrimidinium salts with carbanions. 1-Methylpyrimidinium salts, when reacting in ethoxide/ethanol yield with the carbanion of diethyl malonate yield 1,2-dihydro-2-oxonicotinic esters; with the carbanion of malononitrile 2-amino-3-cyanopyridines are obtained, and with the carbanion of ethyl cyanoacetate 2-amino-3-(ethoxycarbonyl)pyridines (74RTC223) (Scheme 5). It has been observed that quaternization of the pyrimidine ring is necessary to achieve ring transformation; with pyrimidines, not being quaternized does not react with ethyl cyanoacetate and diethyl malonate (Scheme 6). All these pyrimidine ring transformations can be explained by an initial addition of the nucleophile to the electron-deficient position 6, ring opening of the intermediary 1,6-dihydro compound and ring cyclization by internal



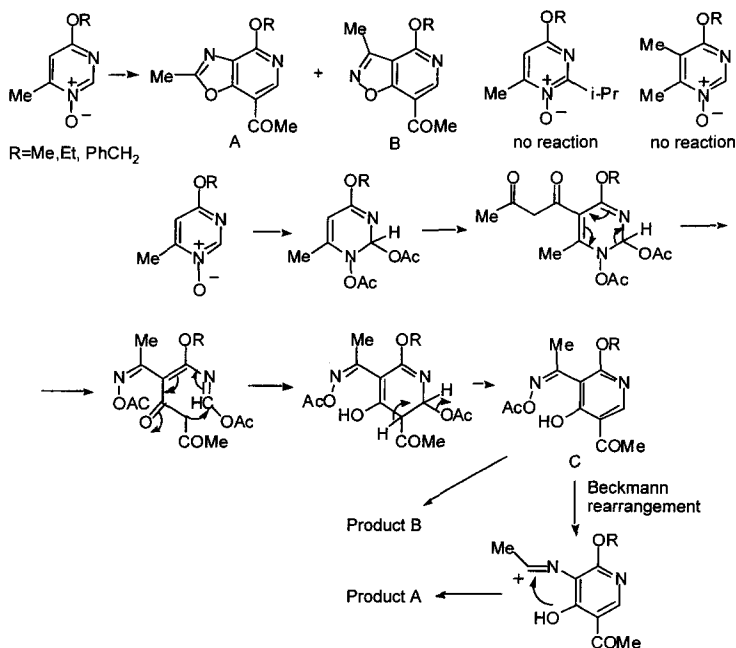
Scheme 7



Scheme 8

addition of nitrogen across the ethoxycarbonyl moiety or the cyano group. For the description of the reaction course with malonitrile, see Scheme 7. In the reaction with cyanoacetate the cyclization is favored by addition across the cyano group instead of elimination of the alkoxy group.

Other examples of CN/CC replacement are observed in reactions of 1-phenylpyrimidin-2(1H)-one with active methylene compounds, such as diethyl malonate and benzoylacetate, giving in good yield 2-oxo-1,2-dihydro-3-pyridinecarboxylate and 3-benzoylpyridin-2(1H)-one, respectively (84CPB2942, 87H2223) (Scheme 8). In a similar way 4,6-dimethyl-1-phenylpyrimidin-2(1H)-one, 4,6-dimethyl-1-phenylpyrimidine-2(1H)-thione and 4,6-dimethyl-1-phenyl-2-phenylimino-1,2-dihydropyrimidine yield with malonitrile 2-amino-4,6-dimethyl-3-pyridinecarbonitrile. In a similar way 2,3-diarylpyrimidin-4(3H)-thiones give with malonitrile CN/CC replacement (84H763) (Scheme 8). The reaction takes a similar course as described in Scheme 7.

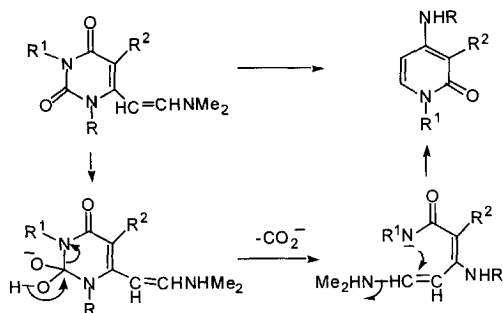


Scheme 8a

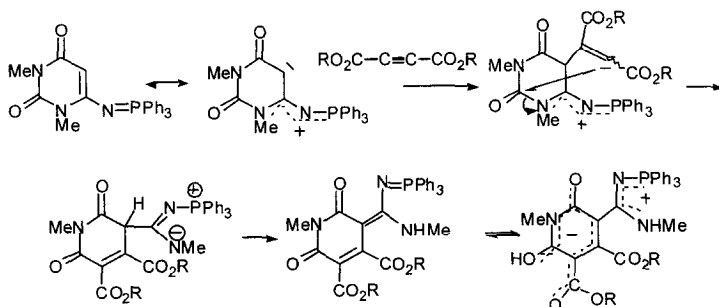
Replacement of the N-1-C-6 moiety by two C-C atoms has been found in the reaction of 4-alkoxypyrimidine 1-oxides with diketene and acetic anhydride in chloroform, yielding a mixture of oxazolopyridines and isoxazolopyridines (Scheme 8a) (88CPB168).

The ring transformation does not occur when the 2- or 5-position is blocked by an alkyl group. Starting material was then recovered. Evidently both the 2- and 5-position play a role in the course of the ring transformation. Based on these results it has been proposed that acetic anhydride attacks position 2 yielding a 1,2-diacetoxy-1,2-dihydropyrimidine derivative, in which the enamine carbon at position 5 reacts with diketene into the 5-acetylacetylpyrimidine derivative. Ring opening, recyclization and aromatization gives the 4-hydroxypyridine 5-ketoxime intermediate C. Cyclization gives the isoxazolopyridine derivative B. The formation of the oxazolopyridine requires a Beckmann rearrangement of the ketoxime, after which cyclization occurs, yielding product A.

There are CN/CC replacements reported which involve the participation of a two-carbon side-chain, present as substituent in the pyrimidine system. An example is the formation of 4-alkylaminopyridin-2-ones on alkaline hydrolysis of 6-[2-(dimethylamino)vinyl]uracils ( $\text{R} = \text{Me, Ph, CH}_2\text{Ph}$ ;



Scheme 9

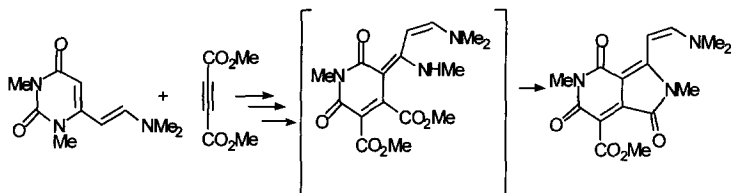


Scheme 10

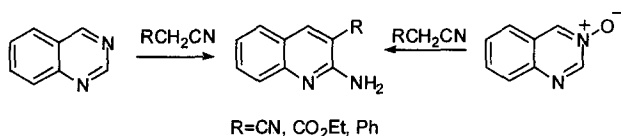
$\text{R}^1 = \text{H}, \text{Me}, \text{Et}, 4\text{-NO}_2\text{C}_6\text{H}_4$ ;  $\text{R}^2 = \text{H}, \text{NO}_2, \text{CN}, \text{CHO}$  (78H739, 88JHC985) (Scheme 9). The pyrimidine-to-pyridine transformation is explained by addition of the base at C-2 and ring opening with loss of carbon dioxide (carbonate). By the recyclization the vinyl carbons are incorporated into the pyridine ring with loss of dimethylamine. The reaction has a broad scope since many different substituents on the ring nitrogen and on the ring carbon at C-5 could be used.

The participation of two side-chain carbons in the ring transformation was also observed when 6-(triphenylphosphoranylidene)amino-1,3-dimethyluracil reacts with dialkyl acetylene dicarboxylate in protic solution, leading to the formation of the zwitterionic pyridine dioxodicarboxylates (86JOC149) (Scheme 10). The reaction course is suggested to involve first a nucleophilic addition of C-5 of the pyrimidine ring to the acetylenic bond forming a zwitterionic species. The ionic terminal carbon in the side-chain attacks the C-2 carbonyl with cleavage of the bond between C-2 and N-1 and expelling the N-1 and C-6 as amidine side-chain (Scheme 10).

A very similar ring transformation was observed when 6-[2-(dimethylamino)vinyl]-1,3-dimethyluracil reacts with dimethyl acetylenedicarboxylate



Scheme 11



Scheme 12

(DMAD) in boiling toluene, the bicyclic compound pyrrolo[3,4-*c*]pyridine being obtained (89CB1673) (Scheme 11).

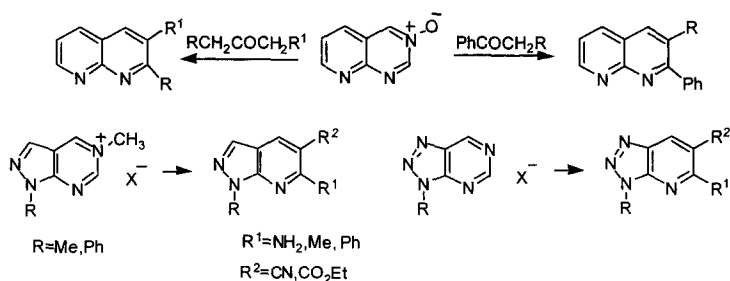
CN/CC replacements were also observed when the pyrimidine ring is part of a bicyclic system. Reaction of quinazoline with active methylene compounds, containing the cyano group (malonitrile, ethyl cyanoacetate, phenylacetonitrile) gave 2-amino-3-R-quinoline (R = CN, CO<sub>2</sub>Et, Ph) (72CPB1544) (Scheme 12). The reaction has to be carried out in the absence of a base. When base is used, no ring transformation was observed; only dimer formation and S<sub>N</sub>H substitution at C-4 was found.

A more detailed study of the reaction with malonitrile revealed that the yields are dependent of the molar ratio malonitrile/quinazoline. The yield increases from 29 (ratio 1.0) to 81% (ratio 2.0), suggesting that the mechanism of the ring transformation involves the contribution of 2 mol of malonitrile. Reaction of quinazoline 3-oxide with the above-mentioned active methylene compounds gives about the same results, although the yields are poor (Scheme 12) (73CPB1943, 75CPB746).

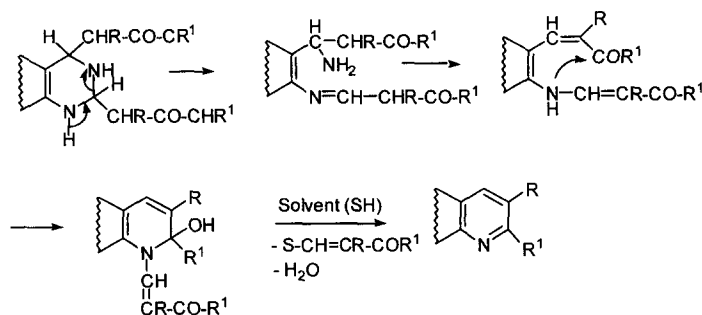
Extension of this work involved reactions of pyrido[2,3-*d*]pyrimidine 3-oxide with alkylphenylketones, providing 2-phenyl-3-R-1,8-naphthyridines (R = alkyl) and with dialkylketones yielding 2,3-dialkyl-1,8-naphthyridines (Scheme 13). The yields are generally rather low (73CPB2643, 75CPB2939, 76CPB3120). Similar conversions are also reported for the 1-methyl- and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium salts (77CPB535) and for the 1,2,3-triazolo[4,5-*d*]pyrimidines (79CPB2861) (Scheme 13).

Concerning the mechanism of the ring transformation it has been argued that the conversion requires addition of 2 mol of the reagent, one for addition to the N-3-C-4 bond and the second one for addition to the





Scheme 13

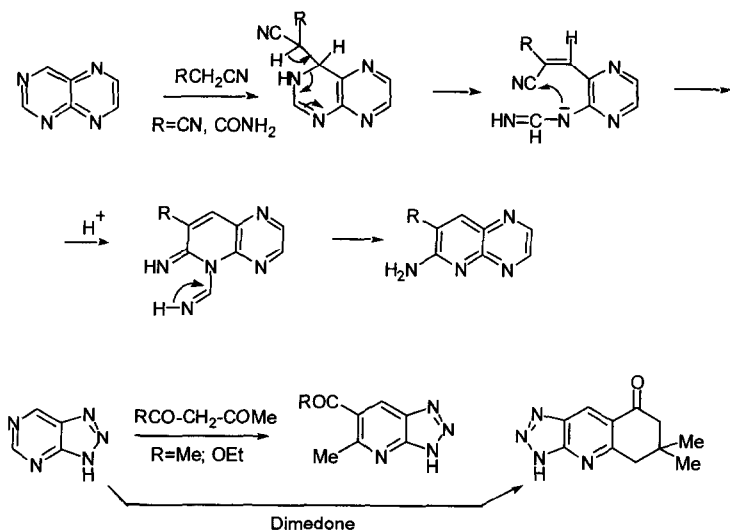


Scheme 14

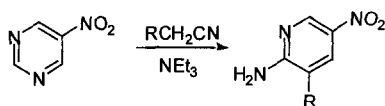
N-1-C-2 bond of the pyrimidine ring. The argument is based on the experimental evidence that the ring transformation does not take place when position 2 is blocked (Scheme 14). This di-adduct will undergo a ring opening between C-2 and N-3; a subsequent ring closure gives a 1,2-dihydropyridine derivative. Loss of the substituent at the nitrogen of the pyridine ring under the influence of the nucleophilic solvent and water leads to aromatization of the pyridine ring.

CN/CC replacement has also been observed on treatment of pteridine with malonitrile or cyanoacetamide 6-amino-7-R-pyrido[2,3,-b]pyrazine ( $R = \text{CN, CONH}_2$ ) being formed (73JCS(1)1615) (Scheme 15). The reaction involves initial addition of the reagent to the N-3-C-4 bond, scission of the dihydro bond between N-3 and C-4 in the covalent adduct, and recyclization. This mechanism is fundamentally different from the mechanism mentioned in Scheme 14, where two molecules of the reagent were used for addition and where the bond breaking takes place between N-1 and C-2.

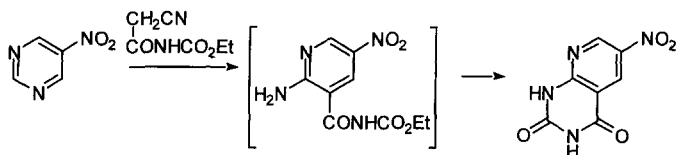
Similar pyrimidine-to-pyridine conversions were also reported for purine and 8-azapurine with C-H active acetonitriles, ethyl acetoacetate, acetylacetone; with dimedone 8-azapurine is converted into triazolotetrahydroquinoline (Scheme 15) (73JCS(P1)1620, S(P1)1625, S(P1)1794).



Scheme 15

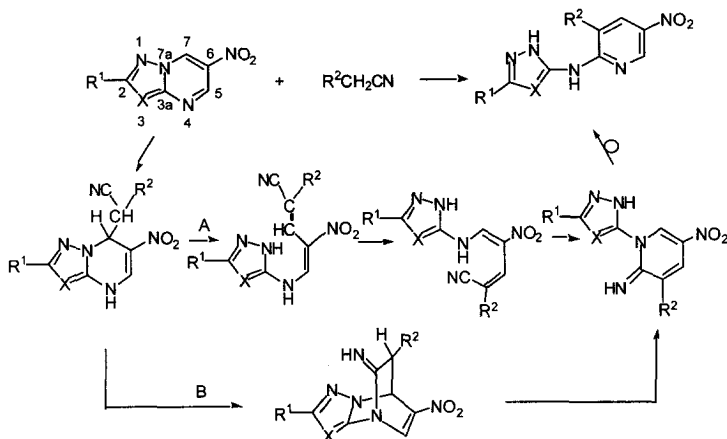


$R = C_6H_4-m-CF_3, C_6H_4-p-NO_2, SO_2Ph, CN, CO_2R$  ( $R = Me, Et, t-Bu$ ),  $CONR_2$



Scheme 16

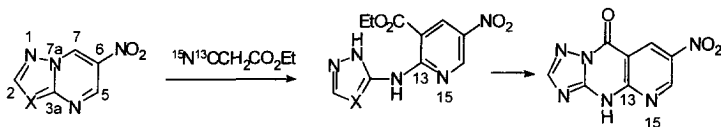
The replacement of the N1-C2-fragment of the pyrimidine ring by a C-C fragment was also reported to take place in reactions of 5-nitropyrimidine with CH-active nitriles and ketones. Arylacetonitriles, bearing an electron-withdrawing group in the phenyl ring ( $CF_3$ ,  $NO_2$ ), but also malonitrile, phenylsulfonylacetonitrile, and cyanoesters are effective reagents to cause the formation of 2-amino-5-nitro-3-R-pyridines (83RTC373, 87RTC547) (Scheme 16). The reaction follows the same course as described in Scheme 15. This easy method to introduce substituents at C-3 of 2-aminopyridines opened new ways for further syntheses of interesting



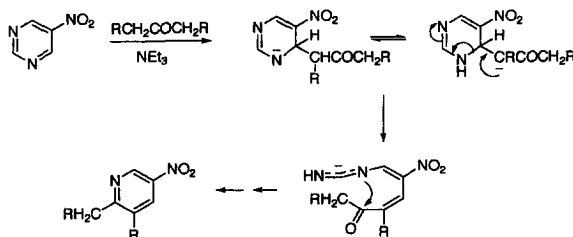
Scheme 17

heterocycles. So gives, for instance, 5-nitropyrimidine with *N*-(cyanoacetyl)carbamate the bicyclic compound 1,2,3,4-tetrahydro-6-nitro[2,3-*d*]pyrimidine-2,4-dione (Scheme 16). Similar conversions have been observed in the reaction of 5-*R*-pyrimidine (*R* = H, Cl, Br, CN) with phenylacetoni-trile in the presence of sodium hydride. 2-Amino-5-*R*-3-phenylpyridines are obtained in good yields (90H1301).

Interesting chemistry has been found on heating of 2-*R*<sup>1</sup>-6-nitro-1,3,7a-triazolo[1,5-*a*]pyrimidines (*R*<sup>1</sup> = H, Me, SMe, CF<sub>3</sub>, Cl, NH<sub>2</sub>, NMe<sub>2</sub>, X = N) with CH-active acetonitriles (*R*<sup>2</sup>COCH<sub>2</sub>CN), such as ethyl cyanoacetate (*R*<sup>2</sup> = CO<sub>2</sub>Et), cyanoacetamide (*R*<sup>2</sup> = CONH<sub>2</sub>), cyanothioacetamide (*R*<sup>2</sup> = CSNH<sub>2</sub>), benzoylacetoni-trile (*R*<sup>2</sup> = CPh) (87KGS857, 90KGS1632). With all these compounds an intriguing rearrangement into 2-(5-*R*<sup>1</sup>-1,2,4-triazolylamino)-3-*R*<sup>2</sup>-5-nitropyridines was observed (Scheme 17). These rearrangement reactions were also observed with six nitropyrazolo[1,5-*a*]pyrimidines, which are activated by the presence of electron-withdrawing substituents (X = CNO<sub>2</sub>, CCO<sub>2</sub>Et). The reaction may be described to take place via adduct formation at C-7, ring opening and ring closure into the 1-[1,2,4-triazol-3-yl](pyrazol-3-yl)-3-*R*<sup>2</sup>-5-nitropyridine (route A). A subsequent Dimroth rearrangement yields 2-[1,2,4-triazolyl(pyrazolyl)amino]-5-nitropyridine. An alternative pathway can be envisaged involving a cycloaddition reaction (Route B) (Scheme 17). Strong support for this mechanism comes from an investigation of the reaction of 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine with doubly-labeled <sup>15</sup>N<sup>13</sup>CCH<sub>2</sub>CO<sub>2</sub>Et. The ethyl ester of 2-(triazolylamino)-5-nitronicotinic acid and its cyclohydration product, i.e. the oxo-azolopyridopyrimidine have in both compounds the



Scheme 18



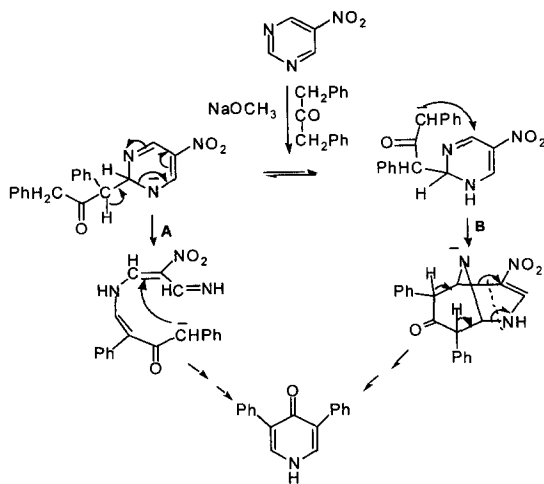
Scheme 19

$^{13}\text{C}$ – $^{15}\text{N}$  fragment in the pyridine ring (90S713, 92TL3695, 93ZOK789) (Scheme 18). All these results unequivocally show that the N1–C2 fragment of the pyridine ring is derived from the cyano group of the reagent.

Reaction of 5-nitropyrimidine with ketones (acetone, diethyl ketone, dibenzyl ketone acetylacetone, acetoacetic ester in the presence of triethylamine also leads to replacement of the N–C moiety of the pyrimidine ring by the C–C fragment of the reagent (Scheme 19). The choice of the base appears to be important since in the presence of potassium hydroxide instead of triethylamine the reaction affords *p*-nitrophenol derivatives (83KGS1393, 87KGS508, S1659). The reaction certainly involves adduct formation at position 6, ring opening and ring closure as indicated in Scheme 19.

#### 4. N–C–C/C–C–C Replacement

Heating of 5-nitropyrimidine with dibenzyl ketone in a solution of dimethyl sulfoxide, containing sodium methoxide gave in 43% yield 3,5-diphenylpyridone-4 (78RTC256) (Scheme 20). Two plausible mechanisms for this N–C–C/C–C–C replacement can be advanced. Route A describes the ANRORC pathway, involving  $\sigma$ -adduct formation at position 2, ring opening and reclosure to the pyridone-4. There is however ample evidence that in reactions of  $\pi$ -deficient nitroaromatics with ketones bicyclic adducts are involved (82JOC1081, 82T1405), therefore route B involving a bicyclic adduct seems a reasonable alternative pathway for explaining formation of pyridone-4 (Scheme 20). Interesting pyrimidine-to-pyridine

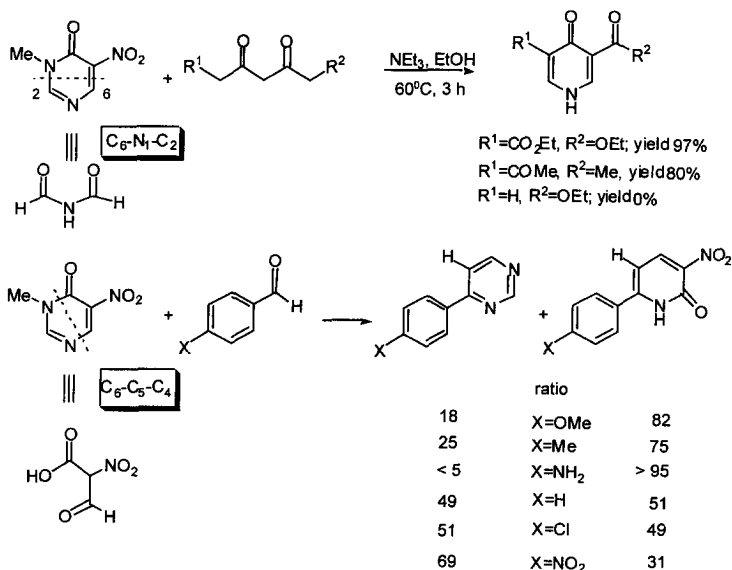


ring transformations are reported to occur when 3-methyl-5-nitropyrimidin-4-(3*H*)-one reacts with 1.1 equivalent of the enolate ions of 1,3-dicarbonyl compounds giving in good yields 3,5-difunctionalized pyridin-4(1*H*)-ones (97S1277, 97JCS(P1)2261). The C-2-N-1-C-6 part of the pyrimidine molecule takes part in the construction of the pyridine ring; it can be considered to act as an activated diformylamine (Scheme 21).

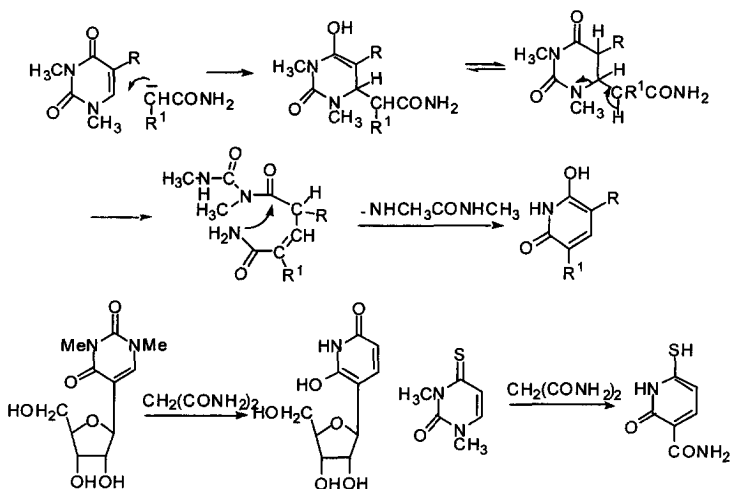
Extension of this work by studying the reaction of 3-methyl-5-nitropyrimidin-4(3*H*)-one with *p*-X-arylketones in the presence of ammonium acetate surprisingly revealed the formation of a mixture of 4-arylpyrimidines and 6-arylpyridin-2(1*H*)-ones (00JCS(P1)27). The ratio between pyridine and pyrimidine formation is dependent on the substituent X. With electron-donating substituents the formation of the pyridin-2(1*H*)-ones is favored, with electron-attracting substituents the formation of the pyrimidine derivatives (Scheme 21). In the formation of the 6-arylpyridin-2(1*H*)-ones the C-4-C-5-C-6 part of the pyrimidinone-4 is the building block in the construction of the pyridine ring. Therefore, the pyrimidinone can be considered as an activated  $\alpha$ -nitroformylacetic acid (Scheme 21).

### 5. N-C-N/N-C-C Replacement

This replacement reaction has been reported to take place on treatment of 5-R-1,3-dimethyluracil derivatives (R = H, Me, CN, F, Br, Cl) with  $\alpha$ -substituted (R<sup>1</sup>) acetamides (R<sup>1</sup> = CONH<sub>2</sub>, CN, COMe, Ph) in basic medium. The reaction provides an easy entry to the synthesis of 3-R-5-R<sup>1</sup>-2,6-dihydroxypyridines (Scheme 22).

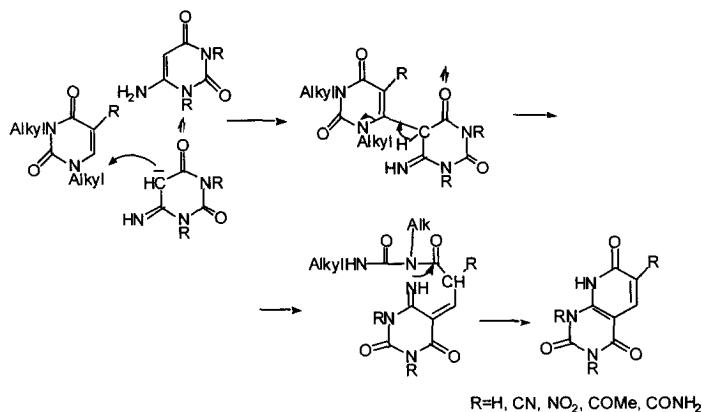


Scheme 21



Scheme 22

An interesting application is the conversion of 1,3-dimethyl-5- $\beta$ -D-ribofuranosyluracil by malonamide into 5- $\beta$ -D-ribofuranosyl-2,6-dihydroxynicotinamide (79JA4423, 80H4076, 81JOC846, 84H289). The ring transformation has been described to occur according to an ANRORC

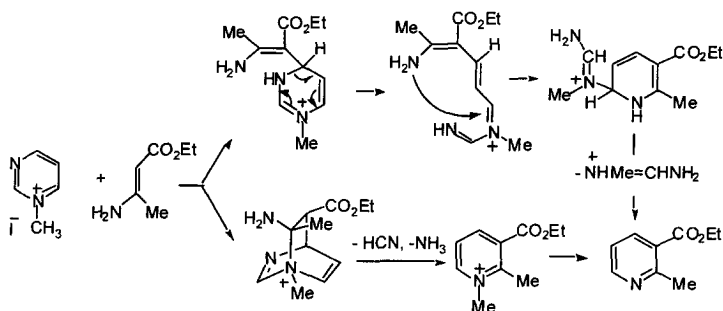


Scheme 23

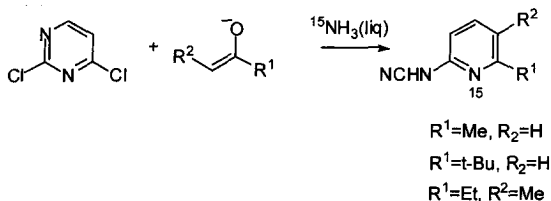
mechanism. First the ambident nucleophile forms a Michael adduct, which undergoes a base-induced ring opening. The intramolecular recyclization yields the 2,6-dihydroxypyridine derivative and dimethylurea. 1,3,6-Trimethyluracil is not reactive. The presence of the substituent at position 6 suppresses the reaction. With the corresponding pyrimidin-4-thione a similar ring conversion occurs (Scheme 22). An interesting application is the reaction of the cyclic ambident nucleophile 6-amino-1,3-dialkyluracil with 5-R-1,3-dimethyluracil ( $R = \text{H}, \text{NO}_2, \text{COMe}, \text{CONH}_2$ ) providing a facile synthesis of 6-R-1,3-dialkylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*, 3*H*, 8*H*) trione (Scheme 23).

An ANRORC mechanism has also been proposed (besides an inverse cycloaddition reaction) in the conversion of 1-methylpyrimidinium iodide into 3-ethoxycarbonyl-2-methylpyridine on treatment with ethyl  $\beta$ -amino-crotonate (95RCB1272) (Scheme 23a). The reaction starts by addition of the  $\beta$ -carbon of the crotonate at the electron-deficient 4-position of the 1-methylpyrimidinium salt, followed by bond breaking of the N3-C4 bond. Recyclization and elimination of the *N*-methylformamidine salt yields the required compound. Since reaction of 1-methylpyrimidinium iodide with ethyl (diethylamino)crotonate also gives—in small yield—3-ethoxycarbonyl-2-methylpyridine which of course cannot be formed via the electrocyclization mechanism, it has been suggested that a cycloaddition reaction can also (partly) be involved. As intermediate the 1,4-cycloadduct is formed, which after removal of ammonia, hydrogen cyanide and nucleophilic removal of the methyl group, yields 3-ethoxycarbonyl-2-methylpyridine (Scheme 23a). For a further discussion of the inverse Diels-Alder reactions, see Section II.B.

A unusual NCN/NCC replacement in which the nitrogen is provided by ammonia and the two carbons by a ketone enolate, is observed in the



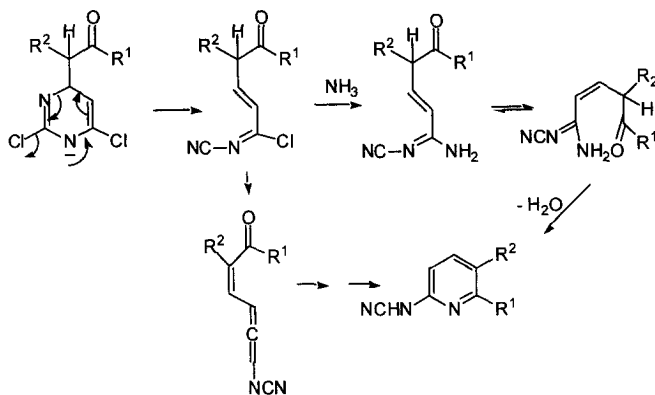
Scheme 23a



Scheme 24

conversion of 2,4-dichloropyrimidine into 6-(cyanamino)pyridines on treatment with potassium enolates of acetone, pinacolone, and 3-pentanone in liquid ammonia. This ring transformation provides a potentially attractive route for synthesizing 6-(cyanamino)pyridines (85JOC3442) (Scheme 24). These nucleophile-induced pyrimidine-to-pyridine transformations can be described to occur according to the  $S_N(\text{ANRORC})$  mechanism. This mechanism has been earlier applied in amino-dehalogenation reactions of halogenoazines (78ACR462), but they always lead to so-called degenerate ring transformations, i.e. transformations in which the ring closure of the open-chain intermediate leads to the *same* heterocycle as present in the starting material (99AHC1). It is interesting that the reaction given in Scheme 24 is the first example of a  $S_N(\text{ANRORC})$  mechanism in which the ring closure leads to a heterocycle, *different* from that of the starting material. The reactions are initiated by addition of the ketone enolates to C-4 of the pyrimidine ring. The covalent  $\sigma$ -adduct being formed undergoes ring cleavage and loss of the chloride ion into the open chain *N*-cyanoimino chloride. Two pathways can be described to obtain the (cyanamino)pyridine derivative. One route describes the aminolysis into *N*-cyanoamidine, followed by a cyclodehydration. An alternative pathway describes the formation of *N*-cyanoketenimine by enolate-induced hydrogen chloride elimination, which undergoes aminolysis and a subsequent





Scheme 25

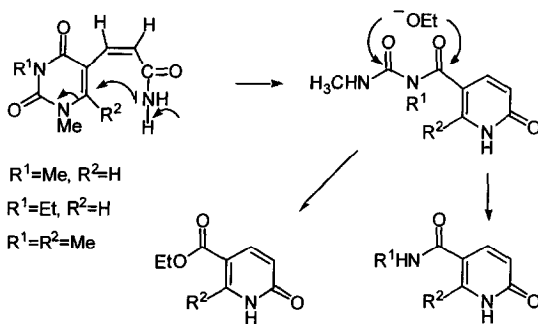
cyclodehydration (Scheme 25). Convincing evidence for this mechanism has been provided by studying the reaction of 2,4-dichloropyrimidine with the pinacolone enolate and  $^{15}\text{N}$  enriched ammonia. 6-(Cyanamino)-2-*t*-butylpyridine is obtained in which the nitrogen of the *pyridine* ring is enriched with nitrogen-15 (see Scheme 24).

#### 6. NCNC/NCCC REPLACEMENT

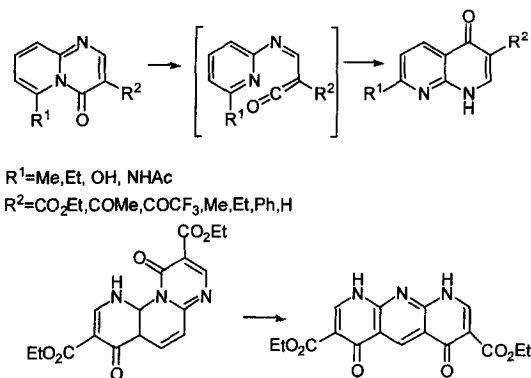
This four-atom replacement was observed in some reactions of uracil derivatives, containing at position 5 a substituent with the CCCN moiety. Treatment of the *Z*-isomer 5-(2-carbamoylviny1)-1,3-dialkyluracil with ethanolic sodium ethoxide gave in good yield 3-ethoxycarbonylpyridin-6(1*H*)-one (84%) together with 3-*N*-methylcarbamoylpyridin-6(1*H*)-one (10%) (85JOC1513) (Scheme 26). The reaction involves an initial attack of the terminal amino group of the side-chain on position 6 of the uracil molecule. C-6-N-1 bond fission and N-C bond formation yield the pyridin-6(1*H*)-one. A subsequent attack of the ethoxide ion on the carbonyl groups of the side-chain yields both pyridin-2-one derivatives (Scheme 26). Similar results were obtained with the *E*-isomer.

#### 7. Isomerizations

There are several ring transformations reported in which the pyrimidine ring, being annelated on the *a*- or *b*-bond with a five- or six-membered ring, may undergo a thermal rearrangement to a pyridine ring being annelated with the same five- or six-membered ring. A thoroughly studied example is the thermally induced nitrogen-to-carbon acyl migration



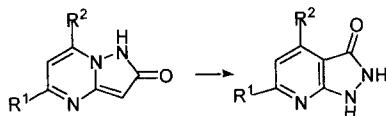
Scheme 26



Scheme 27

of the 6-R-3-R<sup>1</sup>-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidines ( $R = \text{Me, Et, OH, NHAc}$ ;  $R^1 = \text{CO}_2\text{Et, COMe, COCF}_3, \text{Me, Et, Ph, H}$ ) into the 7-R-3-R<sup>1</sup>-5,6,7,8-tetrahydro-1,8-naphthyridin-4-ones (75TL1019, 77JCS(P1)789, 79H1407, 80JCS(P1)27, 91H1455) (Scheme 27). The rearrangement requires the presence of a substituent at position 6. Since the group at C-6 and the oxo group at C-4 are in plane, the C-4-C-5 bond is stretched and subjected to strain (72AC2405). Strain relieve is the driving force for the isomerization into the 1,8-naphthyridine derivatives. This isomerization has been suggested to occur via the ketene intermediate. The nitrogen-to-carbon acyl migration has also been observed in the isomerization of pyrimido[1,2-a][1,8]-naphthyridine into an thyridine derivative (Scheme 27).

Another example of this behavior is the base-induced rearrangement of pyrazolo[1,5-a]pyrimidines ( $R = \text{H}, R^1 = \text{Me}$ ;  $R = \text{Me}, R^1 = \text{Me, Ph}$ ;  $R = \text{CF}_3, R^1 = \text{Me, Ph}$ ) into pyrazolo[3,4-b]pyridines (83PJC1377). The



Scheme 28

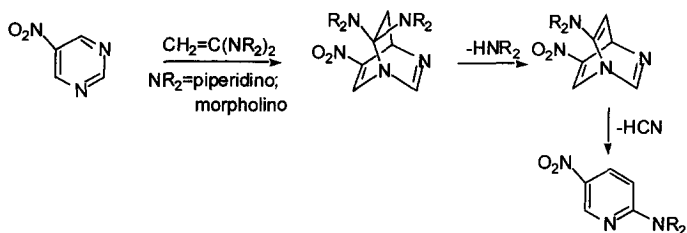
rearrangement involves base addition, bond breaking between carbon and the bridgehead nitrogen of the pyrimidine ring and recyclization, liberating the base (Scheme 28).

## B. HETERO DIELS-ALDER CYCLOADDITION

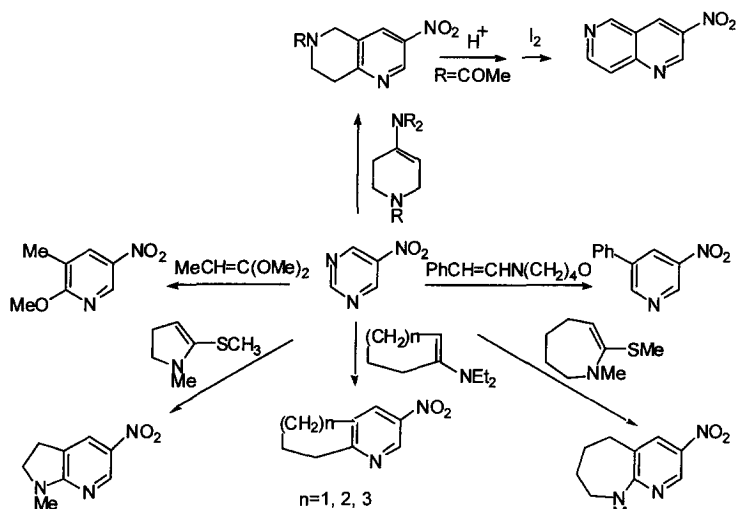
The hetero Diels-Alder [4+2] cycloaddition (HDA reaction) is a very efficient methodology to perform pyrimidine-to-pyridine transformations. *Normal* (NHDA) and *Inverse* (IHDA) cycloaddition reactions, intramolecular as well as intermolecular, are reported, although the IHDA cycloadditions are more frequently observed. The NHDA reactions require an electron-rich heterocycle, which reacts with an electron-poor dienophile, while in the IHDA cycloadditions a  $\pi$ -electron-deficient heterocycle reacts with electron-rich dienophiles, such as O,O- and O,S-ketene acetals, S,S-ketene thioacetals, N,N-ketene acetals, enamines, enol ethers, ynamines, etc.

### 1. Intermolecular IHDA Cycloadditions Involving C-N/C-C Replacements

5-Nitropyrimidine, when subjected to a reaction with the enamines 1,1-bis(morpholino)ethene or 1,1-bis(piperidino)ethene, gives in reasonable yields (about 50%) 2-morpholino-5-nitropyridine and 2-piperidino-5-nitropyridine, respectively. The over-all reaction describes the replacement of the N-C fragment of the pyrimidine ring by two carbon atoms of the dienophile. As intermediate has been postulated a regiospecific cycloadduct, which is formed by addition of the ethylene carbon atoms over the N-1/C-4 positions of the pyrimidine ring; the carbon carrying both dialkylamino groups exclusively adds to N-1 and the ethylene carbon, carrying both hydrogens adds to C-4 (82TL3965, 83JOC2667, 83RTC373, 86JOC67,C71, 89T2693). No products could be isolated which could be formed by a reversed addition. A subsequent *retro* Diels-Alder reaction involving loss of dialkylamine and subsequent rearomatization by elimination of hydrogen cyanide yields the 2-piperidino(morpholino)-5-nitropyridine (Scheme 29). The preference for this regiospecific addition of the enamines across N-1/C-4 of 5-nitropyrimidine was correctly predicted by FMO perturbation theory (86JOC4070).



Scheme 29



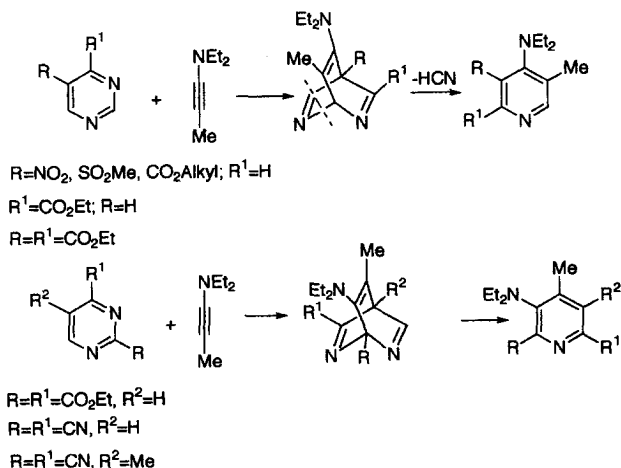
Scheme 30

Extension of this work by reacting 5-nitropyrimidine with O,O-ketene acetals and with other cyclic and non-cyclic enamines showed that also with these electron-rich dienophiles the addition is regioselective and gives rise to the formation of 2-mono- or 2,3-disubstituted 5-nitropyridines (Scheme 30). Thus, reaction of 5-nitropyrimidine with the cyclic N,S-ketene acetals 4,5-dihydro-1-methyl-2-methylthiopyrrole and 4,5,6,7-tetrahydro-1-methyl-2-methylthioazepine gives in low yields 2,3-dihydro-1-methyl-5-nitropyrido[2,3-*b*]pyridine and the 5,6,7,8-tetrahydro-9-methyl-3-nitropyrido[2,3-*b*]azepine, respectively (89T2693) (Scheme 30).

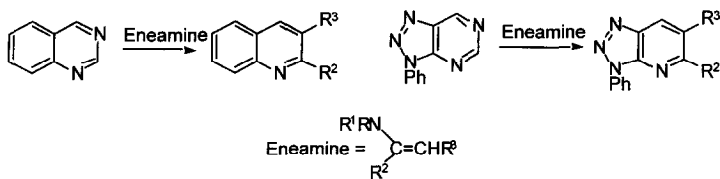
These results show that inverse Diels–Alder reactions of pyrimidines open an easy access to a number of differently substituted pyridines and especially to compounds, in which the carbocyclic ring and the heterocyclic rings are annelated on the *b* position of pyridine. An interesting illustrating example

of synthetic interest is the preparation of the not easily accessible 3-nitro-1,6-naphthyridine (00AHC285). The synthesis involves the formation of a tetrahydronaphthyridine derivative, formed by a cycloaddition between 5-nitropyrimidine and 1-acetyl-4-pyrrolidino-1,2,5,6-tetrahydropyridine; acid hydrolysis gave 3-nitro-5,6,7,8-tetrahydro-1,6-naphthyridine that by oxidation with iodine yielded 3-nitro-1,6-naphthyridine (89T2693, 02THC1) (Scheme 30).

Cycloaddition with ynamines shows a different behavior. Reaction of 5-R-pyrimidine ( $\text{SO}_2\text{CH}_3$ ,  $\text{CO}_2\text{Alkyl}$ ) with diethylaminopropyne gives 5-R-3-methyl-4-diethylamino-pyridine. This 3,4,5-substitution pattern indicates that the addition of the triple bond of the dienophile has occurred regioselectively across C-2/C-5 instead of N-1/C-4, as observed with electron-rich olefines. The rearomatization occurs by elimination of hydrogen cyanide from the cycloadduct (72LAC39, 74LAC1190, 80JHC1111, 85JOC270, 86JOC67) (Scheme 31). This difference of addition behavior between enamines and ynamines is not quite evident. A somewhat confusing feature of these types of rearrangement is that the mode of the addition is dependent on the position, type, and number of electron-withdrawing substituents present in the pyrimidine ring. Whereas the cycloaddition of 4- and 5-ethoxycarbonylpyrimidine and of 4,5-di-(ethoxycarbonyl)pyrimidine with diethylamino propyne affords 4-diethylamino-3-methyl-ethoxycarbonylpyridines, in case of 2,4-di-(ethoxycarbonyl)-, 2,4-dicyano- and 2,4-dicyano-5-methylpyrimidine, a reversed addition across C-2/C-5 takes place leading to a 3-diethylamino-4-methylpyridine derivatives (74LAC1190, 80JHC1111) (Scheme 31). In case of 4,6-di(ethoxycarbonyl)pyrimidine a



Scheme 31



Scheme 32

mixture of 4-diethylamino-3-methyl- and 3-diethylamino-4-methylpyridine derivatives was obtained (74LAC1190, 80JHC1111).

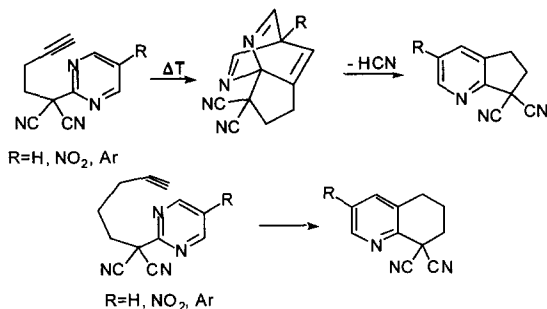
The bicyclic system quinazoline undergoes intermolecular inverse cycloaddition reactions with enamines  $\text{RR}_1\text{NCR}_2=\text{CHR}_3$  ( $\text{RR}_1=(\text{CH}_2)_3$ ,  $\text{R}_2=\text{Ph}$ ,  $\text{R}_3=\text{H}$ ) yielding 2,3-disubstituted quinolines.

Similarly, reaction of 3-Ph-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine with  $\text{RR}_1\text{NCR}_2=\text{CHR}_3$  ( $\text{NRR}_1=\text{piperidino}$ , morpholino,  $\text{R}_2\text{R}_3=(\text{CH}_2)_3$ ,  $(\text{CH}_2)_4$ ,  $\text{R}_2=\text{Ph}$ , Et,  $\text{R}_3=\text{H}$ , Me) gave triazolopyridines (91CPB282) (Scheme 32).

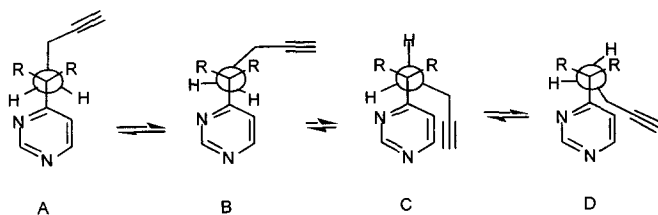
## 2. Intramolecular IHDA Cycloadditions Involving C–N/C–C Replacements

Intramolecular IHDA cycloadditions leading to pyrimidine-to-pyridine ring transformations take place, when at position 2 or 5 of the pyrimidine ring a dienophilic tether is present containing an alkyne bond at the  $\delta$ - or  $\varepsilon$ -position. A proper length of the tether connecting the diene and the dienophile provides substantial entropic assistance and enhances the intramolecular activity (80CR63, 84OR1). In all these transformations the cycloaddition of the alkyne bond takes place across the C-2/C-5 position. It was found that these reactions are very useful entries for constructing pyridines annelated to carbo- or heterocyclic rings (91THC111).

Experiments show that 2-(pent-4-yn-1-yl)pyrimidines react slowly at elevated temperature ( $>200^\circ\text{C}$ ) into 6,7-dihydro-5*H*-1-pyridines. Surprisingly, 2-(pent-4-yn-1-yl)pyrimidines containing on the  $\alpha$  position of the side-chain cyano groups, i.e. 5-*R*-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines ( $\text{R}=\text{H}$ ,  $\text{NO}_2$ , Ar) react at considerable lower temperature ( $130^\circ\text{C}$ ) and give in high yield the corresponding 7,7-dicyano-6,7-dihydro-5*H*-1-pyridines (89T5151) (Scheme 33). The reaction involves a cycloadduct formed by addition of the triple bond across the C-2/C-5 position, followed by HCN elimination. This remarkable rate enhancement observed in the formation of the 7,7-dicyano-6,7-dihydro-5*H*-1-pyridines can be explained in several ways. It is suggested that the presence of the electron-attracting cyano groups on the  $\alpha$ -position of the side-chain enhances the electrophilicity of the pyrimidine ring and consequently increases the reactivity



Scheme 33



Scheme 34

towards the electron-rich triple bond. Another possible explanation is the occurrence of a so-called “scissoring” Thorpe–Ingold effect (21JCS305) or “gem-dialkyl” effect (60JOC701, 61JA1368), attributing the enhanced reactivity to an increase of the angle between both cyano groups ( $\phi_1$ ) due to their electron repulsion. This leads consequently to reduction of the internal  $C_2-C_\alpha-C_\beta$  ( $\phi_2$ ) bond angle forcing the reacting sites in closer proximity ( $\phi_2$  in Pyr-H >  $\phi_2$  in Pyr-CN) (Scheme 34).

Another argument which possibly plays a role is the change of conformational equilibria between the side-chain and the pyrimidine ring when cyano groups are present in the side-chain (Scheme 34). The presence of large cyano groups ( $R=CN$ ) causes in the unreactive *anti*-periplanar conformation A and the *anti*-clinal conformation B a much greater steric repulsion with the pentynyl group than in case of  $R=H$ . This leads for  $R=CN$  to a greater population of the *syn*-clinal and -periplanar

conformations C and D, respectively. The result is that in case of  $R = CN$  on the average in time the dienophile is more in the vicinity of the azadiene moiety and therefore may lead to a higher reactivity for the compounds carrying the cyano groups (Scheme 34). The rate increase, as observed in the intramolecular Diels–Alder reactions of  $\alpha,\alpha$ -disubstituted furfuryl methyl fumarates, has also been explained by the higher population of the *syn* rotamers (88TL2429).

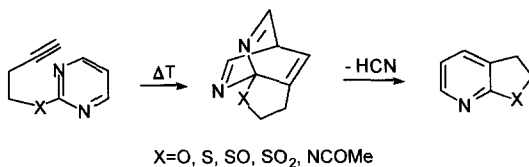
Crystallographic studies of 5-*p*-nitrophenyl-2-(pent-4-yn-1-yl)pyrimidine clearly showed that this compound is present in the *anti*-planar rotamer A/B ( $R = H$ ); 2-(1,1-dicyanopent-4-yn-1-yl)-5-nitropyrimidine is present in its *syn* conformation C/D ( $R = CN$ ) (91JOC2411). These results unequivocally prove that conformational effects are important to explain the observed rate enhancement of the dicyano compound. Measuring the bond angles  $C-2-C\alpha-C\beta$  in both crystalline compounds, it was found that in the dicyano compound the internal bond angle  $\phi_2$  is about  $5^\circ$  smaller than  $\phi_2$  in the dicyanoalkynyl pyrimidine derivative. All these results lead to the conclusion that the Thorpe–Ingold effect certainly contributes to the rate enhancement of the dicyano compound, although its effect is not large. Molecular mechanics calculations indeed show that the *syn* conformation of the 1,1-dicyanopentynyl compound has the lowest energy (91JOC2411). Furthermore, MNDO calculations indicate a higher electron-withdrawing effect of the dicyanoalkyne group, as revealed by a lower transition state energy explaining the enhanced reactivity of the dicyanopyrimidine (91JOC2411).

When measuring the reaction rate of the conversion of a series of 5-(*p*-X- $C_6H_4$ )-2-(1,1-dicyanopentynyl)pyrimidines ( $X = OMe, Me, H, Cl, Br, NO_2$ ) into the corresponding pyridines and making a Hammett plot of  $\log k_X/k_H$  against  $\sigma$ -values for the *para* substituent X, a linear relationship is found with a  $\rho$ -value of +0.06. This positive low value of  $\rho$  shows that the reaction has indeed the character of an inverse Diels–Alder reaction and that in the rate determining formation of the cycloadduct hardly any charge separation is involved. Thus a two step reaction via an zwitterionic intermediate does not seem likely (89T6891).

The relative ease of the reaction with the (1,1-dicyanopentynyl)pyrimidines induced studies of the reaction of 5-R-2-(1,1-dicyanohex-5-yn-1-yl)pyrimidine ( $R = H, NO_2, Ar$ ). They react with more difficulty, due to the longer tether between diene and dienophile leading to a decreased entropic assistance. At a considerable higher temperature than observed for the (1,1-dicyanopentynyl)pyrimidines (210 °C instead of 130 °C and 8,8-dicyano-5,6,7,8-tetrahydroquinolines are formed (89T5151) (Scheme 33).

These intramolecular IHDA pyrimidine-to-pyridine ring transformations are also successfully applied to synthesize bicyclic heterocycles, containing a





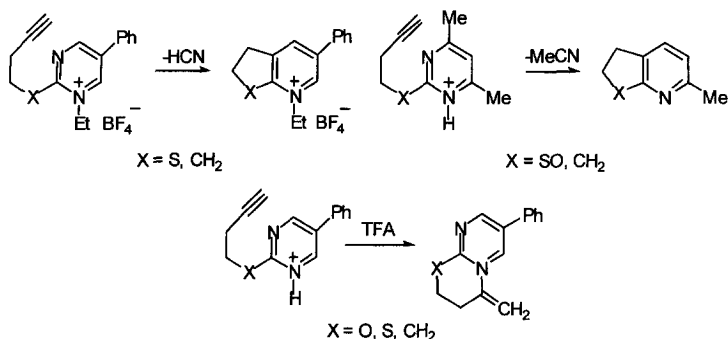
Scheme 35

five-membered heterocyclic ring which is *b*- or *c*-annellated to the pyridine ring. On heating in nitrobenzene (180–210 °C) 2-(but-3-ynyl)pyrimidine (Scheme 35, X=O) gives 2,3-dihydrofuro[2,3-*b*]pyridine in good yield (87TL1589, 89T803). The introduction of a nitro group at position 5 of the pyrimidine ring did not lead to a considerable increase of the reaction rate. Although the rate of addition should be considerably favored by the presence of a nitro group, probably its steric effect decreases the rate of the addition. When a methyl group is present at position 4(6) a mixture of 2,3-dihydrofuro[2,3-*b*]pyridine and its 6-methyl derivative is present (ratio 1:1.8). In all these conversions a tricyclic intermediate has been proposed. This intermediate has, however, never been isolated or detected by spectroscopic measurements. The products can be explained by loss of hydrogen cyanide or in case of the 4(6) methyl derivative by loss of hydrogen cyanide and acetonitrile (Scheme 35).

Similar transformations were also found on heating of 2-(but-3-ynylthio)pyrimidine (X=S) and 2-(but-3-ynylsulfonyl)pyrimidine (X=SO<sub>2</sub>), 2,3-dihydrothieno[2,3-*b*]pyridine and 1,1-dioxo-2,3-dihydrothieno[2,3-*b*]pyridine, respectively being obtained (Scheme 35).

The compound with X=NH did not yield any product on heating; it only results in decomposition. However, after acetylation of the NH group the 2-(*N*-acetyl-3-butynyl amino)pyrimidine easily converts in high yield into 1-acetyl-2,3-dihydropyrrolo[2,3-*b*]pyridine. Due to the acetylation the pyrimidine becomes less electron-rich, the energy levels between the HOMO and LUMO levels decrease and therefore the pyrimidine ring becomes more reactive. 2-(3-Butynylsulfinyl)pyrimidine (X=SO) decompose on heating, but heating in chloroform at 55 °C at a pressure of 15 kbar gave in high yield the 1-oxo-2,3-dihydrothieno[2,3-*b*]pyridine (89T803) (Scheme 35).

Considerable rate enhancements are observed upon quaternization of the pyrimidine ring, due to its electron-deficiency. Heating of the 1-ethyl-2-(pent-4-yn-1-yl)-5-phenylpyrimidinium tetrafluoroborate (X=CH<sub>2</sub>) at 180 °C for 15 min (!) gave in a more or less quantitative yield 1-ethyl-6,7-dihydro-3-phenyl-5*H*-1-pyridinium salt (X=CH<sub>2</sub>) (90T595) (Scheme 36). A similar reaction was also observed with the 2-(butynylthio)pyrimidinium salt (X=S).



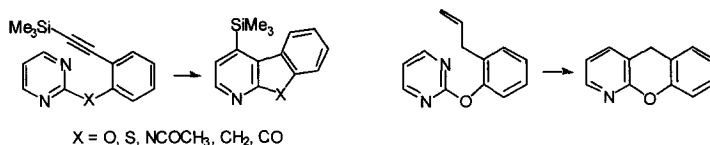
Scheme 36

Rate enhancement could also be promoted when dissolving the pyrimidine derivative in trifluoroacetic acid. This is of particular interest for those pyrimidine derivatives which cannot be quaternized due to the presence of sterically hindering groups adjacent to the ring nitrogen atom. So gives the 2-(3-butynylsulfinyl)-4,6-dimethylpyrimidinium salt ( $X = SO$ ) under rather mild conditions (reflux in trifluoroacetic acid) 2,3-dihydro-6-methyl-1-oxothieno[2,3-*b*]pyridine ( $X = SO$ ) (Scheme 36). A disadvantage to run the reactions in acid is that cycloamination occurs as a side-reaction ( $X = S, O, CH_2$ , Scheme 36).

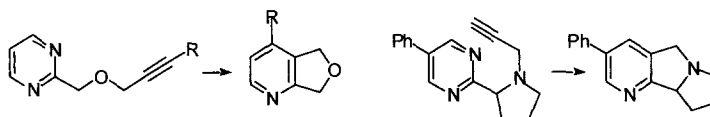
The Diels–Alder methodology can also be applied in the synthesis of tricyclic heterocycles, as was demonstrated by reactions of 2-(2-trimethylsilylethynylphenyl- $X$ )pyrimidines ( $X = O, S, NCOMe, CH_2, CO$ ). They are converted in good yield on heating at 160°C into tricyclic annelated pyridines (89T6511) (Scheme 37). A similar reaction was found with the 2-(2-allylphenoxy)pyrimidines affording azaxanthenes (79H665) (Scheme 37).

Compounds containing a heteroatom in the  $\beta$ -position of the side-chain, like 2-(propynyloxymethyl)pyrimidines ( $R = H, SiMe_3$ ) and 5-phenyl-2-[2-(1-pro-2-ynyl)pyrrolidin-2-yl]pyrimidine react smoothly at 140°C to give 5,7-dihydrofuro[3,4-*b*]pyridine (89T5151) and 3-phenylpyrido[3,2-*c*]pyrrolizine, respectively (Scheme 38) (92JOC3000).

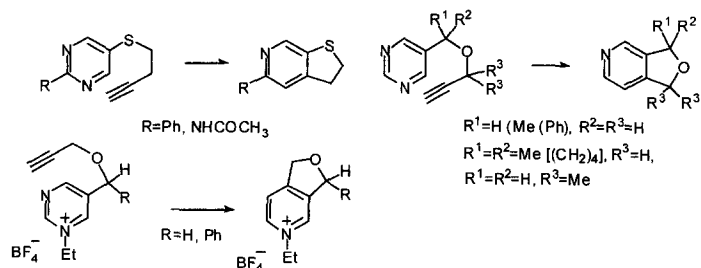
Whereas in all previously mentioned inverse cycloaddition reactions [*b*]-fused pyrido annelated systems are formed, some reactions are described which lead to [*c*]-pyridine annelated bicyclic systems. 5-(Butynylthio)pyrimidines ( $R = Ph, NHCOCH_3$ ) give on heating at 180°C in nitrobenzene 5-*R*-2,3-dihydrothieno[2,3-*c*]pyridines (89T803). 5-Propynyloxymethylpyrimidines also readily undergo cycloaddition into 1,3-dihydrofuro[3,4-*c*]pyridines (89T5151) (Scheme 39). Considerable rate enhancements were observed with quaternized pyrimidinium salts. Whereas



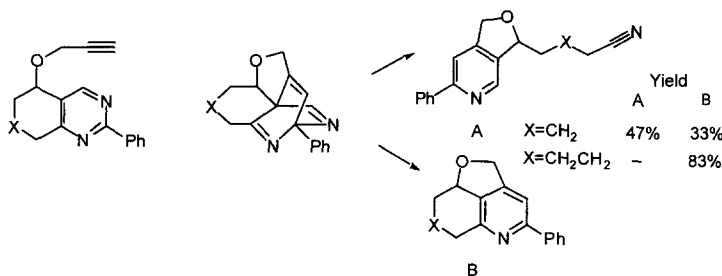
Scheme 37



Scheme 38

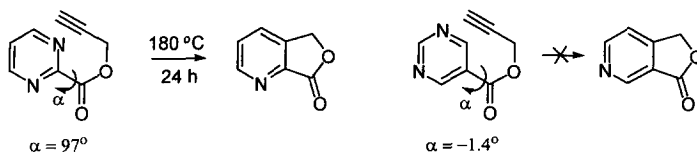


Scheme 39



Scheme 39a

the reaction of 1-ethyl 5-(2-propynyloxymethyl)pyrimidinium tetrafluoroborates only requires heating in nitrobenzene at 110 °C for 1.5 h to give *N*-ethyl-1,3-dihydrofuro[3,4-*c*]pyridinium tetrafluoroborate (Scheme 39), the reaction condition for the unquaternized compound is heating at 140 °C during 10–15 h (depending on substituent R) (89T5151, 90T595). Substitution at the  $\alpha$ - or  $\gamma$ -position in the tether results in somewhat enhanced rates.



Scheme 40

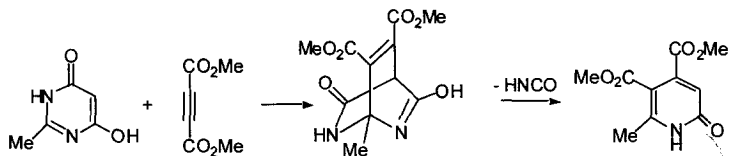
As an extension of this reaction the intramolecular cycloaddition of 5-propynyloxycycloalkanepyrimidines was studied. It was found that bi- and tricyclic annelated pyridine derivatives are formed by expulsion of either  $\text{X-CH}_2\text{-CN}$  and/or  $\text{HCN}$ , respectively. A marked selectivity in the product formation was observed, depending on the size of the cycloalkane ring. With cyclohexapyrimidines a mixture of A and B is formed, while with the cycloheptapyrimidine derivative exclusive formation of the tricyclic compound B takes place (92T1643, 92T1657) (Scheme 39a).

All previous examples show that pyrimidines containing at position 2 or 5 the appropriate alkynyl substituent, are able to undergo inverse Diels-Alder reactions, yielding with expulsion of hydrogen cyanide a pyridine derivative. An interesting exemption of this "general" rule has however been observed when the intramolecular Diels-Alder reaction was studied of 2-(pro-2-ynyloxycarbonyl)pyrimidine and its isomer the 5-(pro-2-ynyloxy carbonyl)-pyrimidine. The 2-isomer gave on heating in nitrobenzene at  $180^\circ\text{C}$  in good yield furo[3,4-*b*]-7(5*H*)-one, whereas the 5-isomer was found to be completely unreactive! (Scheme 40).

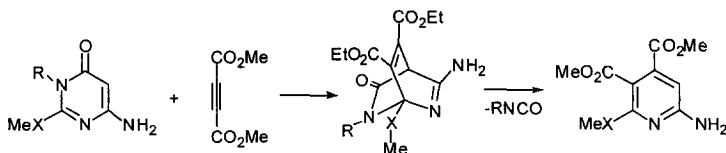
Although HOMO-LUMO calculations show that the 2-isomer is somewhat more reactive than the 5-isomer, the energy difference is relatively small and therefore cannot explain the total inertness of the 5-isomer. A conformational study shows that the difference in reactivity is due to a completely different conformation of both compounds. In the 2-isomer the side chain has about an angle of  $90^\circ$  with the plane of the pyrimidine ring, whereas the side-chain in the 5-isomer is more or less planar with the ring (Scheme 40). Thus, the 2-isomer has a more reactive conformation, since in this conformer the triple bond is located in the right orientation above the plane of the ring, making bond making between C-2 and C-5 possible. Thus conformational analyses of both compounds do indeed predict the order of reactivity, and are in good agreement with the experimentally observed order of reactivity (92JOC3000).

### 3. Intermolecular NHDA Cycloadditions Involving N-C/C-C Replacements

NHDA cycloaddition reactions require an electron-rich heterodiene. Therefore, pyrimidines, which take part in a NHDA reaction needs to,

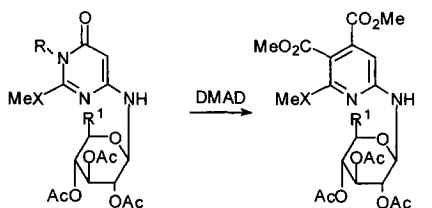


Scheme 41



R=H, X=O; R=H, X=S

R=Me, X=O; R=Me, X=S

R<sup>1</sup>=H, X=O, SR<sup>1</sup>=OAc; X=O, S

Scheme 42

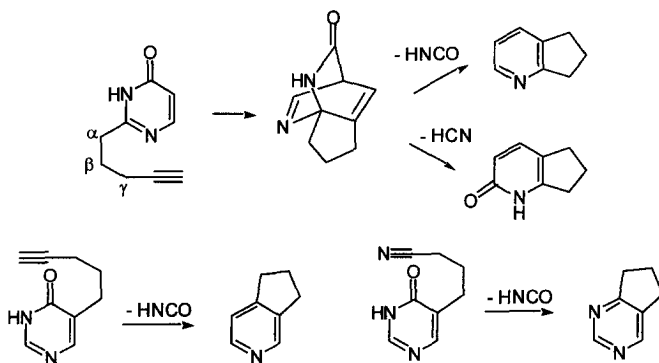
contain electron-donating groups, such as hydroxy or amino groups. Intermolecular as well as intermolecular cycloadditions of pyrimidines with electron-poor alkynes as dienophiles are reported, although less frequently than IHDA reactions.

One of the few examples of an intermolecular NHDA cycloaddition is the reaction of 2-methyl-4-hydroxypyrimidin-6-one with DMAD. A CN/CC replacement takes place yielding dimethyl 2-methyl-3,4-dicarboxypyridin-6-one (70JCS(CC)1103) (Scheme 41). The reaction involves a cycloadduct, formed by an addition between DMAD and the C-2/C-5 position of the pyrimidine ring. A retro Diels-Alder reaction with loss of HCNO (cyanic acid) yields the pyridin-6-one. In a somewhat similar way 6-aminopyrimidin-4(3*H*)-one derivatives react with DMAD into the corresponding 2-aminopyridine derivatives (94T10345, 96T5845). The reaction was successfully used to synthesize 2-glucosylaminopyridines. The formation of these products was rationalized as a result of a NHDA reaction between

the aminopyrimidone and the electron-poor DMAD (Scheme 42). The possible formation of *N*-methylpyridone-2 by extrusion of cyanamide from the cycloadduct was never observed. Semi-empirical calculations using the PM3 method, determining the activation energies for the transition states and the heat of formation for the products, support the results of the experimental work (96T13721). The formation of dicarboxypyridines has also been reported in reactions of the uracil derivatives 6-(triphenylphosphoranylidene)amino-1,3-dimethyluracil (see Scheme 9) and 6-[2-(dimethylamino)vinyl]-1,3-dimethyluracil (see Scheme 10). They have been postulated to react with DMAD via a carbanionic intermediate.

#### 4. Intramolecular NHDA Cycloadditions Involving N-C/C-C Replacements

An intramolecular NHDA reaction was observed during thermolysis of 2-pentynyl- and 5-pentynylpyrimidin-4-ones; *b*- and *c*-annulated cyclopentanopyridines are formed, respectively (75JCS(CC)502, 77JCS(CC)663, 78JCS(P1)1293, 83JHC1407). The reaction involves a cycloadduct which can undergo a retro Diels-Alder aromatization either by elimination of HCN and/or cyanic acid (HNCO) (Scheme 43). A similar reaction occurs when in the tether a cyano group is present;  $\gamma$ -cyanobutylpyrimidin-4-one gives cyclopenta pyrimidine (Scheme 43). In this reaction the C-N part of the pyrimidine ring is replaced by the C-N part of the side-chain. One deals here with a so-called degenerate ring transformation reaction (99AHC1). This reaction has been used as key step in the total synthesis of actinidine (81JCS(P1)1909).



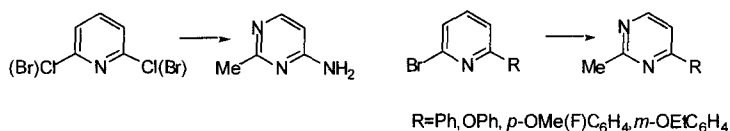
Scheme 43

### III. Pyridine-to-pyrimidine Ring Transformation

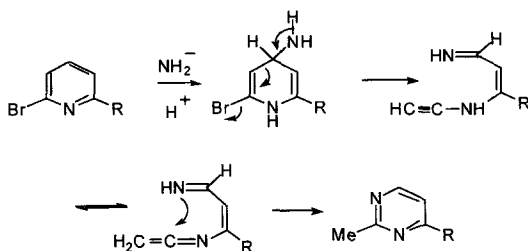
The number of papers describing ring transformations of pyridines into pyrimidines is quite limited. A well-studied reaction is the conversion of 2,6-dibromo(chloro)pyridine into 4-amino-2-methylpyrimidine on treatment with potassium amide in liquid ammonia (65RTC1569, 68TL5945) (Scheme 44). 2,6-Difluoropyridine does not undergo this ring transformation reaction; amino-defluorination at position 2(6) is the sole reaction. In order to investigate the influence of substituents on the scope of the ring transformation a large number of 6-R-2-bromopyridines were investigated ( $R = \text{NH}_2$ ,  $\text{NHPh}$ ,  $\text{CONH}_2$ ,  $\text{NMePh}$ ,  $\text{Me}$ ,  $\text{Ph}$ ,  $\text{OEt}$ ,  $\text{OPh}$ ,  $p\text{-R}'\text{-C}_6\text{H}_4\text{O}$  [ $\text{R}' = \text{OEt}$ ,  $\text{F}$ ],  $m\text{-OEtC}_6\text{H}_4\text{O}$ ). It was found that the ring transformation only occurs in quite limited cases. Only the 2-bromo-6-Ph-, 6-OPh- and 6-(substituted- $\text{C}_6\text{H}_4\text{O}$ )-pyridines could be converted into the corresponding pyrimidine derivatives in reasonable yields (40–50%) (69RTC1391) (Scheme 44).

It is evident that in this ring transformation the C-3–C-4 bond in the pyridine ring has undergone fission. This bond breaking very probable occurs in the covalent  $\sigma$ -adduct at C-4. After ring opening the imino-acetylene derivative is formed; it is in equilibrium with the iminoketenimine, in which cyclization easily occurs (Scheme 45).

The use of the amide ions in these reactions leads sometimes to unexpected side reactions, since besides addition amide ions can also act as a deprotonation agent. An illustrating example is the formation of



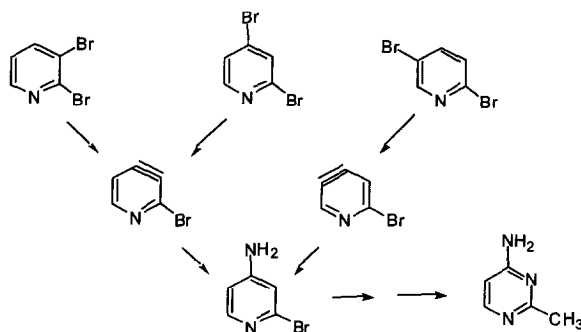
Scheme 44



Scheme 45

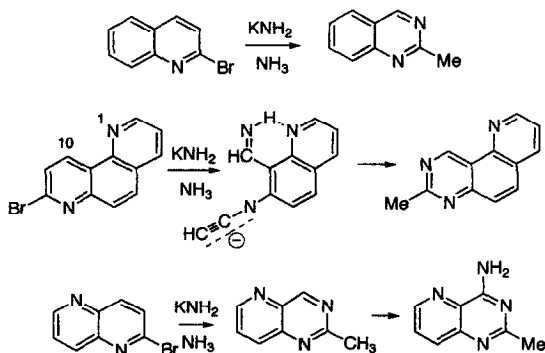
4-amino-2-methylpyrimidine from all three isomeric dibromo compounds, i.e. 2,3-dibromo-, 2,4-dibromo- and 2,5-dibromopyridine, when they are treated with potassium amide in liquid ammonia. The reaction is explained by the intermediate formation of 4-amino-2-bromopyridine, being obtained by a hetaryne mechanism, involving a bromo-3,4-didehydropyridine. This hetaryne is formed by an initial amide-induced deprotonation of the hydrogen present on the carbon adjacent to the one, carrying the bromo atom, followed by debromination (66RTC803) (Scheme 46). The formation of 4-amino-2-methylpyrimidine from 4-amino-2-bromopyridine can be explained according to the route described in Scheme 45.

This pyridine-pyrimidine ring transformation has also been observed on treatment of 2-bromoquinoline with potassium amide in liquid ammonia, 2-methylquinazoline being obtained (67RTC187). Similarly, 8-bromo-1,7-phenanthroline gives 2-methyl-1,3,5-triazaphenanthrene (83JHC447)



Scheme 46

51



Scheme 47



(Scheme 47). An interesting feature is that this product is only obtained after working up of the reaction mixture. NMR spectroscopy proves that in the  $\text{KNH}_2/\text{NH}_3$ , the anionic 7-ethynylaminoquinoline-8-alimine is present, formed by an addition of the amide ion at position 10 and ring opening. In this anionic stage no cyclization can occur; the cyclization only takes place during work-up. NMR evidence for the formation of an open-chain ethynylamino compound was also observed previously during the ring transformation of pyrimidines into *s*-triazines (73JOC2682).

Amide-induced pyridine-pyrimidine transformation is also reported with 2-bromo-1,5-naphthyridine. 2-Methyl-4-amino-1,3,5-triazanaphthalene is obtained, together with its 4-amino derivative. The presence of the amino group at position 4 is certainly due to a  $\text{S}_\text{N}\text{H}$  amino-dehydrogenation in preformed 2-methyl-1,3,5-triazanaphthalene (63RTC997, 73RC459, 94MI1).

## REFERENCES

- 21JCS305 C. K. Ingold, *J. Chem. Soc.*, 305 (1921).  
60JOC701 N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).  
60MI1 F. Brody and P. R. Ruby, in "Pyridine and Derivatives",  
(E. Klingsberg, ed.), p. 47 (1960) Interscience, New York. Part I.  
61JA1368 P. von and R. Schleyer, *J. Am. Chem. Soc.*, **83**, 1368 (1961).  
63RTC997 W. Czuba, *Recl. Trav. Chim. Pays Bas*, **82**, 997 (1963).  
65RTC1569 H. J. den Hertog, H. C. van der Plas, M. J. Pieterse, and J. W. Streef,  
*Recl. Trav. Chim. Pays Bas*, **84**, 1569 (1965).  
66RTC803 J. W. Streef and H. J. den Hertog, *Recl. Trav. Chim. Pays Bas*, **85**, 803  
(1966).  
67RTC187 H. J. den Hertog and D. J. Buurman, *Recl. Trav. Chim. Pays Bas*, **86**,  
187 (1967).  
68TL5945 J. W. Streef and H. J. den Hertog, *Tetrahedron Lett.*, 5945 (1968).  
69RTC1391 J. W. Streef and H. J. den Hertog, *Recl. Trav. Chim. Pays Bas*, **88**, 1391  
(1969).  
70AJC625 D. J. Brown and B. T. England, *Aust. J. Chem.*, **23**, 625 (1970).  
70JCS(CC)1103 A. E. A. Porter and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*,  
1103 (1970).  
71RTC1246 H. C. van der Plas, H. Jongejan, G. Geurtsen, and M. C. Vollerling,  
*Recl. Trav. Chim. Pays Bas*, **90**, 1246 (1971).  
72AC2405 R. Sasvari, J. Csouka-Horvai, and K. Simon, *Acta Crystallogr.*, **28B**,  
2405 (1972).  
72CPB1544 T. Hagashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.*, **20**, 1544  
(1972).  
72LAC39 H. Neunhoeffer and G. Werner, *Liebigs Ann. Chem.*, 39 (1972).  
73CPB1943 T. Hagashino, Y. Nagano, and E. Hayashi, *Chem. Pharm. Bull.*, **21**,  
1943 (1973).  
73CPB2643 T. Hagashino and E. Hayashi, *Chem. Pharm. Bull.*, **21**, 2643 (1973).

- 73JCS(P1)1615 A. Albert and H. Mizuno, *J. Chem. Soc., Perkin Trans. 1*, 1615 (1973).  
73JCS(P1)1620 A. Albert and W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, 1620 (1973).  
73JCS(P1)1625 A. Albert and W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, 1625 (1973).  
73JCS(P1)1794 A. Albert and W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, 1794 (1973).  
73JOC2682 J. P. Geerts and H. C. van der Plas, *J. Org. Chem.*, **43**, 2682 (1973).  
73MI1 H. C. van der Plas, in "Ring Transformations of Heterocycles" Vol. 1 and 2 (1973) Academic Press, London and New York.  
73RC459 J. Pomorski and H. J. den Hertog, *Rocz. Chem.*, **47**, 459 (1973).  
74LAC1190 H. Neunhoeffer and G. Werner, *Liebigs Ann. Chem.*, 1190 (1974).  
74MI1 A. J. Boulton, in "Lectures in Heterocyclic Chemistry" (R. N. Castle and L. B. Townsend, eds.), Vol. 2, S-45. Heterocorporation, Orem, Ut, 1974.  
74MI2 H. C. van der Plas, in "Lectures in Heterocyclic Chemistry" (R. N. Castle and L. B. Townsend, eds.), Vol. 2, S-83. Heterocorporation, Orem, Ut, 1974.  
74RTC223 E. A. Oostveen and H. C. van der Plas, *Recl. Trav. Chim. Pays Bas*, **83**, 223 (1974).  
75CPB746 T. Hagashino, K. Suzuki, and E. Hayashi, *Chem. Pharm. Bull.*, **23**, 746 (1975).  
75CPB2939 T. Hagashino, K. Suzuki, and E. Hayashi, *Chem. Pharm. Bull.*, **23**, 2939 (1975).  
75JCS(CC)502 P. G. Sammes and R. A. Watt, *J. Chem. Soc., Chem. Commun.*, 502 (1975).  
75TL1019 Z. Meszaros and I. Hermecz, *Tetrahedron Lett.*, 1019 (1975).  
76CPB3120 T. Hagashino, Y. Iwai, and E. Hayashi, *Chem. Pharm. Bull.*, **24**, 3120 (1976).  
76RTC104 E. A. Oostveen and H. C. van der Plas, *Recl. Trav. Chim. Pays Bas*, **95**, 104 (1976).  
77AG(E)572 R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **16**, 572 (1977).  
77CPB535 T. Hagashino, Y. Iwai, and E. Hayashi, *Chem. Pharm. Bull.*, **25**, 535 (1977).  
77JCS(CC)663 L. B. Davies, P. G. Sammes, and R. A. Watt, *J. Chem. Soc., Chem. Commun.*, 663 (1977).  
77JCS(P1)789 L. Vsvary-Debreczy, I. Hermecz, Z. Meszaros, P. Dvortsak, and G. Toth, *J. Chem. Soc., Perkin Trans. 1*, 789 (1977).  
78ACR462 H. C. van der Plas, *Acc. Chem. Res.*, **11**, 462 (1978).  
78H33 H. C. van der Plas, *Heterocycles*, **9**, 33 (1978).  
78H739 S. Senda, K. Hirota, Y. Asao, and Y. Abe, *Heterocycles*, **9**, 739 (1978).  
78JCS(P1)1293 L. B. Davies, O. A. Leci, P. G. Sammes, and R. A. Watt, *J. Chem. Soc., Perkin Trans. 1*, 1293 (1978).  
78JHC485 H. C. van der Plas, H. Jongejan, and A. Koudijs, *J. Heterocycl. Chem.*, **15**, 485 (1978).  
78KGS867 H. C. van der Plas, *Khim. Geterotsikl. Soedin.*, 867 (1978).  
78RTC256 P. Barczynski and H. C. van der Plas, *Recl. Trav. Chim. Pays Bas*, **91**, 256 (1978).  
78TL4135 R. S. Sagitullin, A. N. Kost, and G. G. Danagulyan, *Tetrahedron Lett.*, 4135 (1978).

- 79CPB2861 T. Hagashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.*, **27**, 2861 (1979).
- 79H665 T. Jojma, H. Takeshiba, and T. Kinoto, *Heterocycles*, **12**, 665 (1979).
- 79H1407 I. Hermecz and Z. Meszaros, *Heterocycles*, **12**, 1407 (1979).
- 79JA4423 K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. Fox, *J. Am. Chem. Soc.*, **101**, 4423 (1979).
- 79TL1241 L. S. Cook and B. J. Wakefield, *Tetrahedron Lett.*, 1241 (1979).
- 80CR63 G. Brieger and J. N. Bennet, *Chem. Rev.*, **80**, 63 (1980).
- 80H4076 K. Hirota, Y. Kitade, and S. Senda, *Heterocycles*, **14**, 4076 (1980).
- 80JCS(P1)27 I. Hermecz, Z. Meszaros, L. Vsvary-Debreczy, A. Horvath, G. Horvath, and M. Pongor-Csakvari, *J. Chem. Soc., Perkin Trans. I*, 27 (1980).
- 80JHC1111 J. C. Martin, *J. Heterocycl. Chem.*, **17**, 1111 (1980).
- 80WCH491 H. C. van der Plas, *Wiad. Chem.*, **34**, 491 (1980).
- 81AHC141 M. Ruccia, N. Vivona, and D. Spinelli, *Adv. Heterocycl. Chem.*, **29**, 141 (1981).
- 81JCS(P1)1909 L. B. Davies, S. G. Greenberg, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. I*, 1909 (1981).
- 81JOC846 K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. Fox, *J. Org. Chem.*, **46**, 846 (1981).
- 81T3423 A. Kost, S. P. Gromov, and R. S. Sagatullin, *Tetrahedron*, **37**, 3423 (1981).
- 82JCRS113 L. S. Cook, G. Prodhoe, N. D. Venayak, and B. Wakefield, *J. Chem. Res., Synop.*, 113 (1982).
- 82JOC1081 T. L. Su, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **47**, 1081 (1982).
- 82MI1 A. T. Balaban *Pyrylium Salts, Syntheses, Reactions and Physical Properties* (1982) Academic Press, New York.
- 82T3537 G. L' abbe, *Tetrahedron*, **38**, 3537 (1982).
- 82T1405 T. L. Su, K. A. Watanabe, and J. J. Fox, *Tetrahedron*, **38**, 1405 (1982).
- 82TL3965 V. N. Charushin and H. C. van der Plas, *Tetrahedron Lett.*, 3965 (1982).
- 83JHC447 H. J. W. van den Haak, J. P. Bouw, and H. C. van der Plas, *J. Heterocycl. Chem.*, **20**, 447 (1983).
- 83JHC1407 E. Rougeot, H. Moskowitz, and M. Miocque, *J. Heterocycl. Chem.*, **20**, 1407 (1983).
- 83JOC2667 V. N. Charushin and H. C. van der Plas, *J. Org. Chem.*, **48**, 2667 (1983).
- 83KGS1393 Ya. Remennikov, A. A. Kislenko, and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, 1393 (1983).
- 83PJC1377 R. Balicki, *Pol. J. Chem.*, 1377 (1983).
- 83RTC373 V. N. Charushin and H. C. van der Plas, *Recl. Trav. Chim. Pays Bas*, **102**, 373 (1983).
- 84CPB2942 A. Katoh, Y. Omote, and C. Kashima, *Chem. Pharm. Bull.*, **32**, 2942 (1984).
- 84H289 K. A. Watanabe, T. L. Su, K. W. Pankiewicz, and K. Harada, *Heterocycles*, **21**, 289 (1984).
- 84H763 A. Katoh, Y. Omote, and C. Kashima, *Heterocycles*, **22**, 763 (1984).
- 84JHC627 G. L' abbe, *J. Heterocycl. Chem.*, **21**, 627 (1984).
- 84MI1 A. R. Katrizky and C. W. Rees, eds., *Comprehensive Heterocyclic Chemistry*, Vols. 1-8 (1984) Pergamon, Oxford.

- 84OR1 E. Ciganek, *Org. React.*, **32**, 1 (1984).
- 85JOC270 A. T. M. Marcelis, H. C. van der Plas, and S. Harkema, *J. Org. Chem.*, **50**, 270 (1985).
- 85JOC1513 K. Hirota, Y. Kitade, K. Shimada, and Y. Maki, *J. Org. Chem.*, **50**, 1513 (1985).
- 85JOC3442 H. M. Bell, D. R. Carver, J. S. Hubbard, Y. P. Sachdeva, and J. Wolfe, *J. Org. Chem.*, **50**, 3442 (1985).
- 85T237 H. C. van der Plas, *Tetrahedron*, **41**, 237 (1985).
- 86JOC67 A. T. M. Marcelis and H. C. van der Plas, *J. Org. Chem.*, **51**, 67 (1986).
- 86JOC71 D. A. de Bie, B. Geurtsen, and H. C. van der Plas, *J. Org. Chem.*, **51**, 71 (1986).
- 86JOC149 H. Wamhoff, W. Schupp, A. Kirfel, and G. Will, *J. Org. Chem.*, **51**, 149 (1986).
- 86JOC4070 A. T. M. Marcelis, H. C. van der Plas, O. M. W. van den Ham, and J. W. Verhoeven, *J. Org. Chem.*, **51**, 4070 (1986).
- 87H2223 A. Katoh, T. Nishio, and C. Kashima, *Heterocycles*, **26**, 2223 (1987).
- 87KGS508 G. Ya. Remennikov, L. K. Kurilenko, I. V. Boldyrev, and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, 508 (1987).
- 87KGS857 V. L. Rusinov, T. L. Pilicheva, A. A. Tomashov, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, 857 (1987).
- 87KGS1659 G. Ya. Remennikov, L. K. Kurilenko, I. V. Boldyrev, and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, 1659 (1987).
- 87RTC547 A. E. Frissen, A. T. M. Marcelis, G. Geurtsen, and H. C. van der Plas, *Recl. Trav. Chim. Pays Bas*, **106**, 547 (1987).
- 87TL1589 A. E. Frissen, A. T. M. Marcelis, and H. C. van der Plas, *Tetrahedron Lett.*, 1589 (1987).
- 88CPB168 H. Yamanaka, S. Niitsuma, M. Sakai, and T. Sakamoto, *Chem. Pharm. Bull.*, **36**, 168 (1988).
- 88AHC302 V. N. Charushin, O. N. Chupakhin, and H. C. van der Plas, *Adv. Heterocycl. Chem.*, **43**, 302 (1988).
- 88JHC985 Y. Kitade and Y. Maki, *J. Heterocycl. Chem.*, **25**, 985 (1988).
- 88KGS1570 E. V. Babaev, S. I. Bobrovskii, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1570 (1988).
- 88TL2429 M. E. Jung and J. Gervay, *Tetrahedron Lett.*, 2429 (1988).
- 89AHC73 V. N. Charushin, S. G. Alexeev, O. N. Chupakhin, and H. C. van der Plas, *Adv. Heterocycl. Chem.*, **46**, 73 (1989).
- 89CB1673 E. B. Walsh and H. Wamhoff, *Chem. Ber.*, **122**, 1673 (1989).
- 89T803 A. E. Frissen, A. T. M. Marcelis, and H. C. van der Plas, *Tetrahedron*, **45**, 803 (1989).
- 89T2693 A. T. M. Marcelis and H. C. van der Plas, *Tetrahedron*, **45**, 2693 (1989).
- 89T5151 A. E. Frissen, A. T. M. Marcelis, D. G. Buurman, C. A. M. Pollman, and H. C. van der Plas, *Tetrahedron*, **45**, 5151 (1989).
- 89T6511 W. A. W. Stolle, A. T. M. Marcelis, A. Koetsier, and H. C. van der Plas, *Tetrahedron*, **45**, 6511 (1989).
- 89T6891 A. E. Frissen, A. T. M. Marcelis, W. C. Melger, and H. C. van der Plas, *Tetrahedron*, **45**, 6891 (1989).
- 90H1301 S. Ohba, T. Sakamoto, and H. Yamanaka, *Heterocycles*, **31**, 130 (1990).
- 90KGS1632 V. L. Rusinov, T. L. Pilicheva, A. A. Tomashov, G. G. Aleksandrov, E. O. Sidorov, I. V. Karpin, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, 1632 (1990).

- 90S713 O. N. Chupakhin, V. L. Rusinov, T. L. Pilicheva, and A. A. Tomashov, *Synthesis*, 713 (1990).
- 90T595 A. E. Frissen, G. Geurtsen, A. T. M. Marcelis, and H. C. van der Plas, *Tetrahedron*, **46**, 595 (1990).
- 91CPB282 A. Miyashita, N. Taido, S. Sato, and K. Yamamoto, *Chem. Pharm. Bull.*, **39**, 282 (1991).
- 91JOC2411 W. A. W. Stolle, A. E. Frissen, A. T. M. Marcelis, H. C. van der Plas, Y. Wang, L. Haming, and C. H. Stam, *J. Org. Chem.*, **56**, 2411 (1991).
- 91H1455 I. Hermecz, A. Horvath, T. Eros-Takacsy, and B. Podanyi, *Heterocycles*, **32**, 1455 (1991).
- 91THC111 A. T. M. Marcelis and H. C. van der Plas, *Trends Heterocycl. Chem.*, **1**, 111 (1991).
- 92AHC49 N. Vivona, S. Buscemi, V. Frenna, and G. Cusmano, *Adv. Heterocycl. Chem.*, **56**, 49 (1992).
- 92JOC3000 W. A. W. Stolle, A. E. Frissen, A. T. M. Marcelis, and H. C. van der Plas, *J. Org. Chem.*, **57**, 3000 (1992).
- 92T1643 W. A. W. Stolle, J. M. Veurink, A. T. M. Marcelis, and H. C. van der Plas, *Tetrahedron*, **48**, 1643 (1992).
- 92T1657 W. A. W. Stolle, A. T. M. Marcelis, and H. C. van der Plas, *Tetrahedron*, **48**, 1657 (1992).
- 92TL3695 O. N. Chupakhin, V. L. Rusinov, A. A. Tomashov, E. O. Sidorov, and I. V. Karpin, *Tetrahedron Lett.*, 3695 (1992).
- 93ZOK789 O. N. Chupakhin, V. L. Rusinov, A. A. Tomashov, E. O. Sidorov, and I. V. Karpin, *Zh. Org. Khim.*, **29**, 789 (1993).
- 94KGS1649 H. C. van der Plas, *Khim. Geterotsikl. Soedin.*, 1649 (1994).
- 94MI1 O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, California, 1994.
- 94T10345 J. Cobo, C. Garcia, M. Melguizo, A. Sanchez, and M. Nogueras, *Tetrahedron*, **50**, 10,345 (1994).
- 95H(40)441 V. L. Rusinov, O. N. Chupakhin, and H. C. van der Plas, *Heterocycles*, **40**, 441 (1995).
- 95RCB1272 S. P. Gromov and M. A. Rezinkin, *Russ. Chem. Bull.*, **44**, 1272 (1995).
- 96T5845 J. Cobo, M. Melguizo, A. Sanchez, and M. Nogueras, *Tetrahedron*, **52**, 5845 (1996).
- 96T13721 J. Cobo, M. Melguizo, M. Nogueras, A. Sanchez, J. A. Dobado, and M. Nonella, *Tetrahedron*, **52**, 13,721 (1996).
- 97JCS(P1)2261 N. Nishiwaki, H.-P. Wang, K. Matsuo, Y. Tohda, and M. Ariga, *J. Chem. Soc., Perkin Trans. 1*, 2261 (1997).
- 97S1277 N. Nishiwaki, Y. Tohda, and M. Ariga, *Synthesis*, 1277 (1997).
- 99AHC1 H. C. van der Plas, *Adv. Heterocycl. Chem.*, **74**, 1 (1999).
- 99CHC1375 G. G. Danugylyan, L. G. Sahakyan, A. R. Katritzky, and S. Denisenko, *Chem. Heterocycl. Comp.*, **35**, 1375 (1999).
- 00AHC285 M. Wozniak and H. C. van der Plas, *Adv. Heterocycl. Chem.*, **77**, 285 (2000).
- 00JCS(P1)27 N. Nishiwaki, T. Adachi, K. Matsuo, H.-P. Wang, T. Matsunaga, Y. Tohda, and M. Ariga, *J. Chem. Soc., Perkin Trans. 1*, 27 (2000).
- 00KGS698 G. G. Danagulyan and L. G. Sahakyan, *Khim. Geterotsikl. Soedin.*, 698 (2000).

- 00CHC613 G. G. Danagulyan and L. G. Sahakyan, *Chem. Heterocycl. Comp.*, **36**, 613 (2000).
- 00H419 G. G. Danagulyan, L. G. Sahakyan, A. R. Katritzky, and S. Denisenko, *Heterocycles* **53**, 419 (2000).
- 02THC1 H. C. van der Plas, *Targets Heterocycl. Chem.*, **5**, 1–37 (2002).

# Fused Heterocyclo-Quinolines Containing One Nitrogen Atom at Ring Junction: Part 1. Four and Five Membered Heterocyclo-Quinolines

EL-SAYED H. EL-ASHRY\*

*Chemistry Department, Faculty of Science, Alexandria University,  
Alexandria, Egypt*

EL-SAYED I. IBRAHIM<sup>†</sup>

*Chemistry Department, Faculty of Science, Suez Canal University,  
Ismailia, Egypt*

I. Introduction	72
II. Four Membered Heterocyclo-Quinolines with One Heteroatom	73
A. Azetoquinolines	73
1. Azeto[1,2- <i>a</i> ]quinolines	73
III. Four Membered Heterocyclo-Quinolines with Two Heteroatoms	76
A. Thiazetoquinolines	76
1. 1,3-Thiazeto[3,2- <i>a</i> ]quinolines	77
IV. Five Membered Heterocyclo-Quinolines with One Heteroatom	83
A. Pyrroloquinolines	83
1. Pyrrolo[1,2- <i>a</i> ]quinolines	83
2. Pyrrolo[4,5,1- <i>ij</i> ]quinolines	97
3. Pyrrolo[2,1- <i>j</i> ]quinolines	120
V. Five Membered Heterocyclo-Quinolines with Two Heteroatoms	124
A. Pyrazoquinolines	124
1. Pyrazo[1,5- <i>a</i> ]quinolines	124
2. Pyrazo[4,5,1- <i>ij</i> ]quinolines	131
B. Imidazoquinolines	132
1. Imidazo[1,2- <i>a</i> ]quinolines	132
2. Imidazo[1,5- <i>a</i> ]quinolines	136
3. Imidazo[4,5,1- <i>ij</i> ]quinolines	138
C. Oxazoloquinolines	146
1. Oxazolo[3,2- <i>a</i> ]quinolines	146
2. Oxazolo[3,4- <i>a</i> ]quinolines	151
3. Oxazolo[5,4,3- <i>ij</i> ]quinolines	151

\*Corresponding author. Fax: +20-3-4271360; E-mail: eelashry@link.net;  
eelashry60@hotmail.com;

<sup>†</sup>E-mail: sibrahim9@hotmail.com

4. Oxazolo[2,3- <i>j</i> ]quinolines	152
D. Thiazoloquinolines	152
1. Thiazolo[3,2- <i>a</i> ]quinolines	152
2. Thiazolo[3,4- <i>a</i> ]quinolines	160
3. Thiazolo[5,4,3- <i>ij</i> ]quinolines	160
VI. Five Membered Heterocyclo-Quinolines with Three Heteroatoms	162
A. Triazoloquinolines	162
1. 1,2,3-Triazolo[1,5- <i>a</i> ]quinolines	162
2. 1,2,3-Triazolo[4,5,1- <i>ij</i> ]quinolines	164
3. 1,2,4-Triazolo[4,5- <i>a</i> ]quinolines	165
4. 1,2,4-Triazolo[1,5- <i>a</i> ]quinolines	168
B. Thiadiazoloquinolines	173
1. 1,2,4-Thiadiazolo[4,5- <i>a</i> ]quinolines	173
C. Antimonyloxazoloquinolines	173
1. 2,1,3-Antimonyloxazolo[5,4,3- <i>ij</i> ]quinolines	173
VII. Five Membered Heterocyclo-Quinolines with Four Heteroatoms	173
A. Tetrazoloquinolines	173
1. 1,2,3,4-Tetrazolo[1,5- <i>a</i> ]quinolines	175
VIII. Conclusions	177
References	178

## I. Introduction

Many clinically useful therapeutics which contain a quinoline moiety have broad spectra of biological activities. The tricyclic ring systems that incorporate quinoline, whose nitrogen atom at a ring junction, are one of the important classes of compounds. Since the number of publications on such heterocyclo-quinolines with this feature is too many to be included in one review, the present chapter, which includes the recent chemistry and biological aspects of four and five membered-heterocycles, is considered as Part 1. It covers the literature until volume 130 in chemical abstracts. Such heterocycloquinolines can be identified into three categories; (x, y-*a*), (x, y, z-*ij*) and (x, y-*j*) based on the possibility of fusion on the quinoline ring. The x, y and z denote the side of the heterocyclic ring which is fused to the quinoline ring, whereas *a*, *i* and *j* denote the quinoline bonds to which the heterocycle is fused (Fig. 1). Increasing the variation and/or number of heteroatoms in the heterocyclic ring system may increase the number of possibilities of the isomeric structures. The fusion on bond *j* could only exist in case of hydrogenated derivatives, specifically at the bond junction connecting the benzene ring on the pyridine one. For simplification, the double bond in the tricyclic systems are not be shown in Figs. 1 and 2. The tricyclic systems included in this review were classified according to the size of the heterocyclic ring and subdivided according to the number of heteroatoms in those rings.



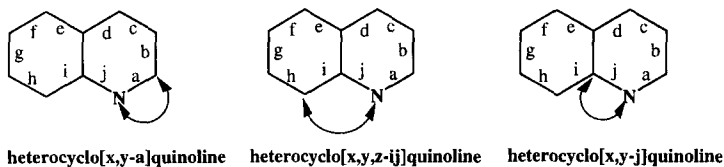


Fig. 1

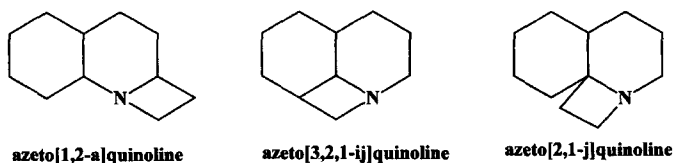


Fig. 2

## II. Four Membered Heterocyclo-Quinolines with One Heteroatom

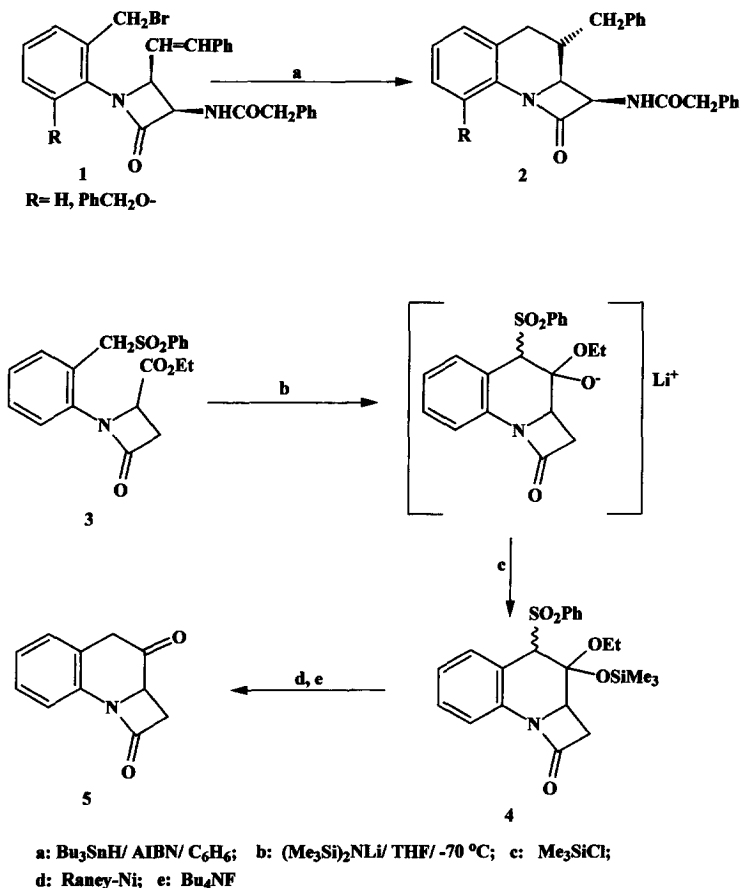
### A. AZETOQUINOLINES

There are three classes of such tricyclic ring system that can be included under this heading of azetioquinolines. However, examples of only one of them have been reported.

#### 1. *Azeto[1,2-a]quinolines*

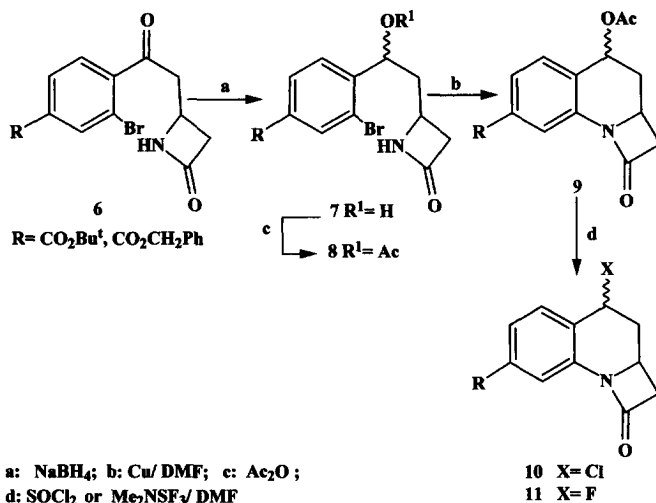
Such ring system can be constructed by two different approaches; either forming the pyridine part of the quinoline ring onto a preformed 1-azetidiny benzene or forming the azetidine ring on the quinoline. Thus, intramolecular free radical cyclization of 2-styrylazetidinone **1** with tributyl tin hydrid ( $\text{Bu}_3\text{SnH}$ ) and  $\alpha,\alpha'$ -azobisisobutyronitrile (AIBN) gave the benzocarbacephems **2** (87CJC104).

Intramolecular cyclization of 2-phenylsulfonylmethyl lactam **3** took place upon reaction with lithium hexamethyldisilazan via generating its  $\alpha$ -sulfonyl carbanion to give a cyclized postulated intermediate that can be quenched with trimethylchlorosilane to afford the stable silyl ketal **4**. The later ketal was desulfonylated by Raney-Ni and desilylated through treatment with tetrabutyl ammonium fluoride ( $\text{Bu}_4\text{NF}$ ) to afford the carbacephem **5** (94M71) (Scheme 1).



Scheme 1

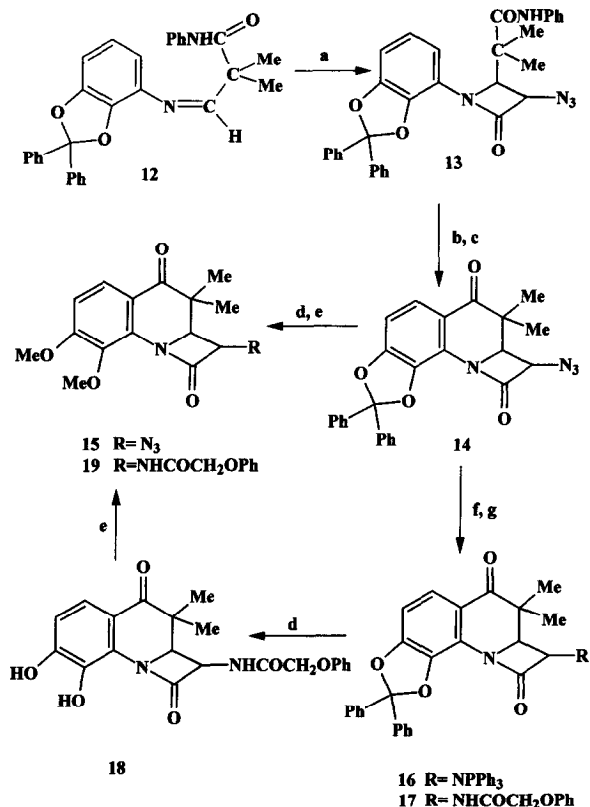
Copper-promoted intramolecular aromatic substitution of a number of azetidinone derivatives **6** has been used for the synthesis of this ring system (83JCS(CC)431, 87JCS(P1)1899). Thus, reduction of azetidinone derivatives **6** (80JOMC9) with  $\text{NaBH}_4$  gave a diastereoisomeric mixture of alcohols **7**. Copper-mediated cyclization of the corresponding acetates **8** in DMF afforded a diastereoisomeric mixture of benzocarbacephems **9**. The cyclization efficiency was effected by the functionalities present on the alkyl part of the ring to be formed and by the steric hindrance in **6**. Chlorination of **9** with  $\text{SOCl}_2/\text{DMF}$  gave **10** as racemic diastereoisomers while the fluorination with dimethylaminosulfur trifluoride (DAST) gave **11** as a single diastereoisomer (87JCS(P1)1899) (Scheme 2).



Scheme 2

Reaction of the imine derivative **12** with triethylamine and azidoacetyl chloride gave **13**. Application of a modified Bischler Napieralski reaction on the lactam **13** by treatment with  $\text{PCl}_5$  in 2,6-lutidine followed by  $\text{SnCl}_4$ , afforded dihydroazeto[1,2-*a*]quinoline-1,4(2*H*)-dione **14**. Its formation was explained by the generation of imidoyl chloride which could give the electrophilic nitrilium ion, by the Lewis acid, that reacts with the aromatic carbon to give imine whose hydrolysis by acid gave **14**. Treatment of **14** with trifluoroacetic acid followed by reaction with diazomethane gave **15**. Reaction of **14** with triphenyl phosphine afforded **16** whose subsequent reaction with phenoxyacetyl chloride gave **17**. Its deprotection gave **18** which upon methylation gave the corresponding dimethoxy derivative **19**. Compound **18** had no antibacterial activity *in vitro* against *Staphylococcus aureus* strain *H* and *Escherichia coli* 7343 (83JCS(P1)1925) (Scheme 3).

Reaction of quinoline **20** with  $\text{EtMgBr}$  followed by methyl chloroformate gave 1-methoxycarbonyl-2-ethylquinoline **21** together with the 4-ethyl regioisomer derivative (71BCJ520). Catalytic hydrogenation of **21** using  $\text{Pd}/\text{C}$  afforded the tetrahydroquinoline derivative that upon decarbamoylation and then acylation with either  $\text{ClCOCH}_2\text{CO}_2\text{Me}$  or diketene afforded **22**. Diazotransfer reaction (86JOC4077) on **22** upon treatment with  $\text{MeSO}_2\text{N}_3$ , DBU gave the diazoamides **23** and **24**. Treatment of **23** with  $\text{Rh}_2(\text{OAc})_4$  afforded the cyclized azetidinone **25** ( $R = \text{CO}_2\text{Me}$ ) as the major product (85%). On the other hand, the major product (88%) from the cyclization of **24** was the pyrroloquinoline **26** (92JOC4404) (Scheme 4).

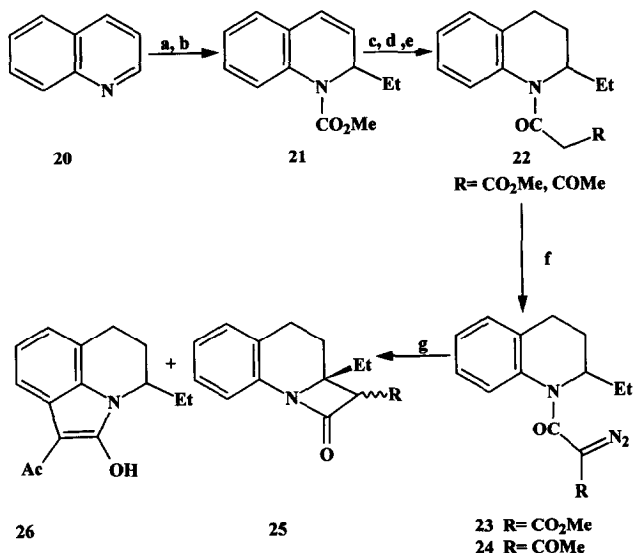


Scheme 3

### III. Four Membered Heterocyclo-Quinolines with Two Heteroatoms

#### A. THIAZETOQUINOLINES

The fusion of four membered-heterocycles with two heteroatoms onto face *a* of the quinoline offers two isomeric combinations of the tricyclic ring system; 1,2-heterocyclo[2,3-*a*]quinoline and 1,3-heterocyclo[3,2-*a*]quinoline. The later one of these two ring systems is the only one that examples of it namely, 1,3-thiazeto[3,2-*a*]quinoline have been reported. Moreover, examples of those fused on faces *ij* or *j* are not known (Fig. 3).



a: EtMgBr/ Et<sub>2</sub>O; b: ClCO<sub>2</sub>Me; c: H<sub>2</sub>/ Pd-C; d: KOH/NH<sub>2</sub>NH<sub>2</sub>/ (CH<sub>2</sub>OH)<sub>2</sub>;  
e: ClCOCH<sub>2</sub>CO<sub>2</sub>Me, or diketene/ Et<sub>3</sub>N; f: MeSO<sub>2</sub>N<sub>3</sub>/DBU; g: Rh<sub>2</sub>(OAc)<sub>4</sub>

Scheme 4

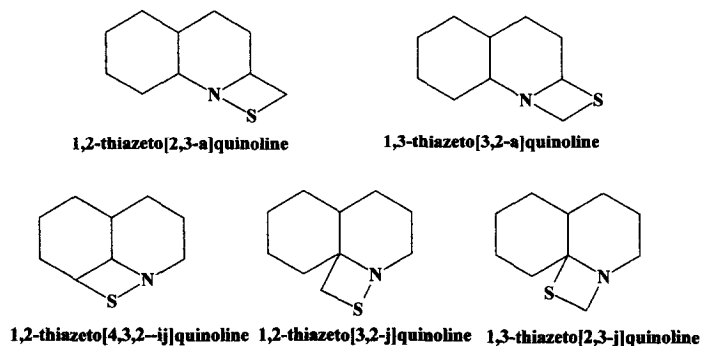
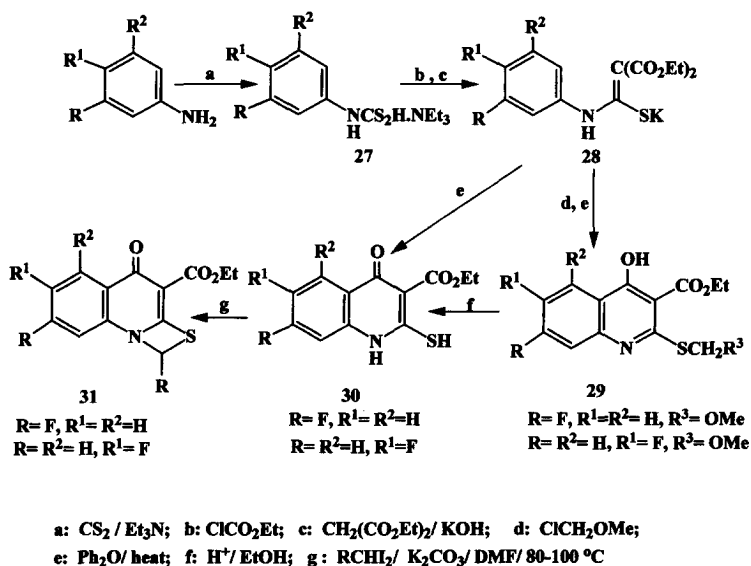


Fig. 3

### 1. 1,3-Thiazeto[3,2-a]quinolines

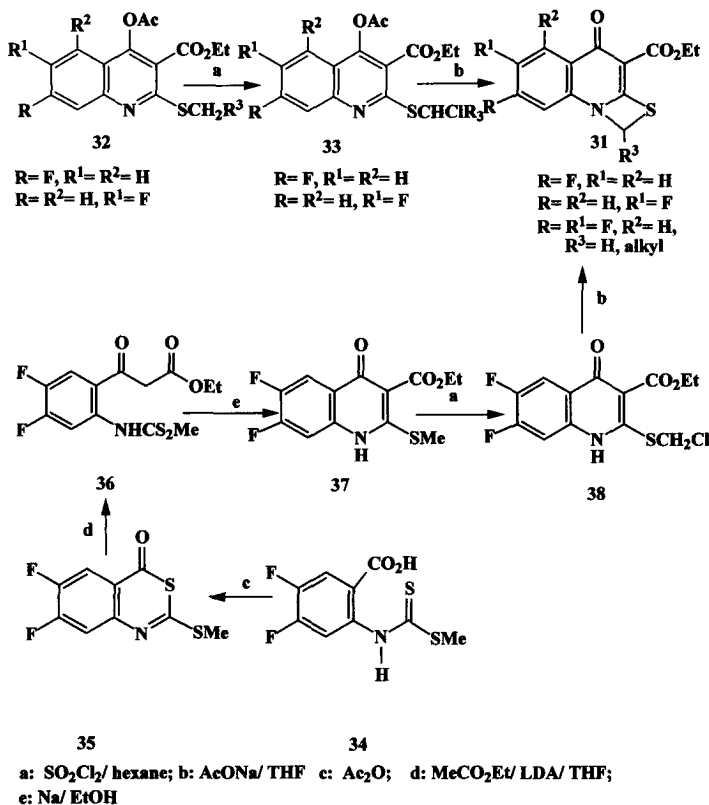
This ring system can be constructed by building one of the two heterocyclic rings on the other preformed ring; the construction of the thiazeto ring on a quinoline moiety or generating a pyridine ring on a



Scheme 5

suitable functionalized phenyl thiazetidine derivative. Thus, reaction of aniline derivatives with carbon disulfide gave the dithiocarbamate derivative **27** which could be transformed to the respective isocyanate that upon treatment with diethyl malonate in presence of KOH gave **28**. Alkylation of **28** with chloromethyl methyl ether afforded the corresponding thioether (93WOP9325532) whose subsequent thermal cyclization gave the regioisomers **29** which upon hydrolysis with acid in ethanol gave **30** that exist in the keto form in the acidic medium. On the other hand, thermal cyclization of **28** by heating in diphenyl ether afforded the regioisomeric quinolines **30** whose cyclization with dihaloalkanes gave the corresponding thiazetoquinolines **31** (92JMC4727, 97JHC1773, 93JAPK0559067) (Scheme 5).

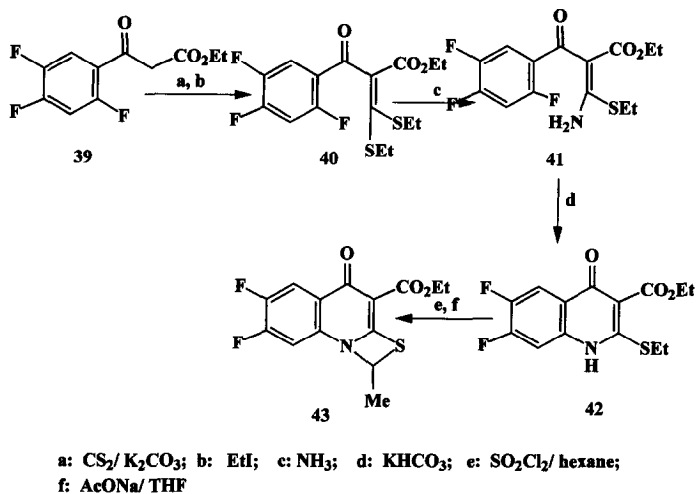
Alternatively, the synthesis of thiazetoquinolines **31** could be achieved by intramolecular cyclization of **33** by heating with sodium acetate or triethylamine. The later compounds were prepared by protection of the hydroxy group in **29** using acetic anhydride to give the corresponding acetyl derivatives **32** which upon chlorination with suluryl chloride gave 2-chloroalkylthioquinolines **33** (93WOP9325532, 96WOP9600217). The required functionalized quinoline was also prepared by reaction of 4,5-difluoroanthranilic acid with carbon disulfide followed by methylation to give the dithiocarbamate **34** which upon treatment with  $Ac_2O$  afforded the



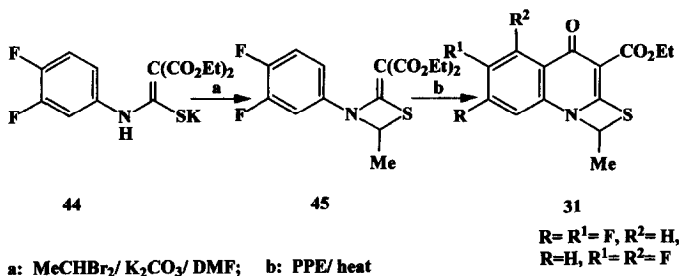
Scheme 6

corresponding benzothiazin-4-one **35**. Treatment of **35** with ethyl acetate in presence of LDA afforded **36** that could be cyclized with sodium ethoxide to give the quinolone derivative **37** which can be transformed to **31** via **38** as above (97JHC1773). A variety of compounds using almost the same procedure were reported in patents for studying the biological activity (91WOP9107412, 92JAPK04356491, 93JAPK0559067, 94JAPK0616678, 94JAPK0616676, 91JAPK03261788) (Scheme 6).

The required quinoline derivative for constructing this ring system can be prepared from ethyl benzoylacetate derivative **39** (91JMC168). Thus, its reaction with CS<sub>2</sub> followed by ethylation gave the dithioacetal **40** (88S792) which upon reaction with ethanolic ammonia gave **41** along with a considerable amount of the respective diamino derivative. Cyclization of **41** with KHCO<sub>3</sub> afforded **42**. Treatment of **42** with sulfonyl chloride followed



Scheme 7



Scheme 8

by heating with sodium acetate in THF afforded thiazetoquinoline **43** (97JHC1773, 93WOP9325532) (Scheme 7).

The second approach is the synthesis of a suitable functionalized thiazitidine followed by constructing the quinoline ring. Thus, cyclization of **44** with a dihaloalkane gave **45** which upon cyclization afforded **26** and **27** (92JMC4727) (Scheme 8).

A review on structure–activity relationship of thiazetoquinolines with 255 references was reported (92MI57). Nucleophilic displacement of the fluorine atom in 7-fluorothiazetoquinoline derivatives with cyclic secondary amine gave compounds interesting for biological activity. Thus, reaction of 3-*tert*-butoxycarbonylaminopyrrolidine with **46** gave the corresponding 7-pyrrolidinyl derivative which upon deprotection by acid and alkali gave

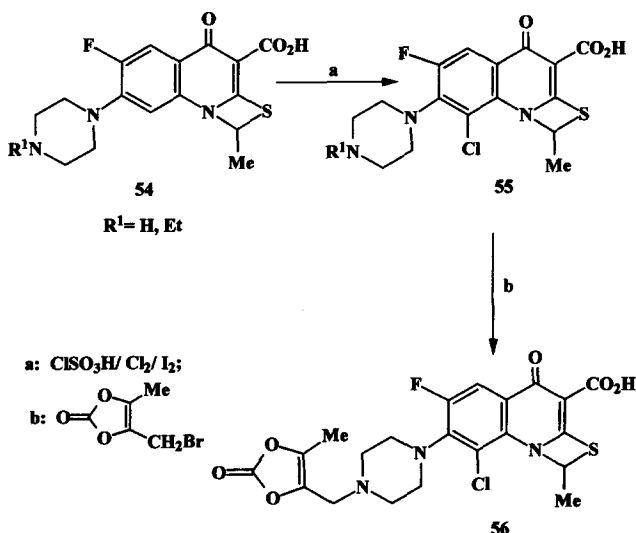


### Scheme 9

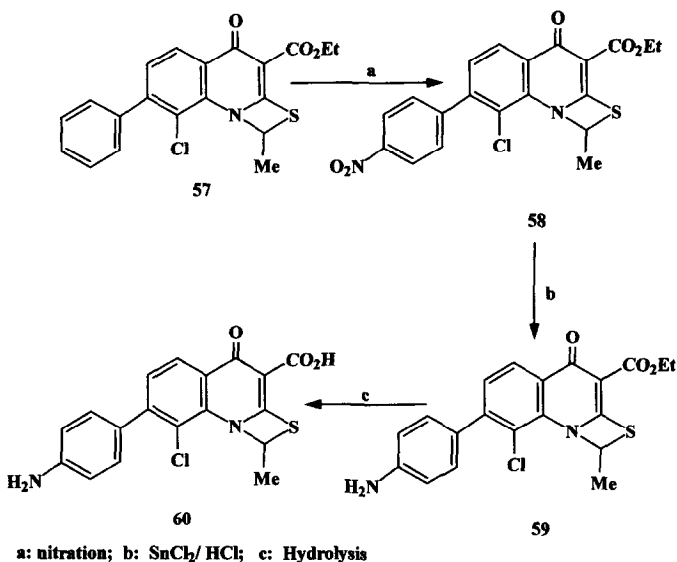
thiazetoquinoline 3-carboxylic acid derivatives such as **52** obtained by reaction with protected aminoacids and then deprotection and repeating the same process gave **53** (93JAPK05117280) as antitumor, antiviral and anti AIDS agents. Some thiazetoquinoline derivatives **53** were reported as neoplasm inhibitors (92JAPK04178326) (Scheme 9).

Hydrolysis of **46** with sulfuric acid and then replacing the 7-fluorine with piperazine afforded **54**, whose potent antibacterial activity and cytotoxicity were similar to ciprofloxacin (89EP315827, 96MI1457, 87GBP2190376). Chlorination of **54** gave the 8-chloro derivative **55** which has an increased antibacterial activity (91JAPK0356489, 90JAPK02174783, 95CPB63). The absolute configuration at C-1 of the thiazetoquinoline ring was confirmed by X-ray analysis (95CPB1238), and it was found to have effect on the antibacterial activity of the compounds. The *S* isomer of **54** which was isolated from the reaction mixture by using HPLC showed a stronger *in vitro* bacterial activity than the *R* isomer (91JAPK03218383, 95CPB1238). Reaction of **55** with 4-bromomethyl-5-methyl-1,3-dioxalan-2-one afforded **56** (89EP315828) as antibacterial. More biological studies were done on **56** as a lipophilic prodrug (91AAC2496) (Scheme 10).

Nitration of the 7-phenyl derivative **57** gave the corresponding *p*-nitrophenyl derivative **58** which upon reduction with  $\text{SnCl}_2/\text{HCl}$  gave the amino derivative **59**. Hydrolysis of **59** afforded **60** which showed antibacterial activity (92WOP9206099, 94WOP9414819) (Scheme 11).



Scheme 10



Scheme 11

## IV. Five Membered Heterocyclo-Quinolines with One Heteroatom

### A. PYRROLOQUINOLINES

Such ring system may be classified into three isomeric structures; pyrrolo [1,2-*a*]quinoline, pyrrolo[4,5,1-*ij*]quinoline and pyrrolo[2,1-*j*]quinoline (Fig. 4).

#### 1. *Pyrrolo*[1,2-*a*]quinolines

This ring system can be constructed by starting with suitable functionalized quinolines that can be readily prepared by reaction of aniline derivatives **61** with diethyl 3-oxoglutarate to afford **62** which upon cyclization with polyphosphoric acid gave the corresponding quinolylacetate **63**. Its reaction with diethyl acetylenedicarboxylate afforded the corresponding pyrroloquinoline **64** whose hydrogenation afforded **65** (87JOC3930). The pyrroloquinoline **66** was prepared from **62** (87SC319) (Scheme 12).

Heating of diphenylcyclopropenone **67** with the cyclic amidine **68** in dimethoxyethane afforded the tricyclic compound **69** that upon heating

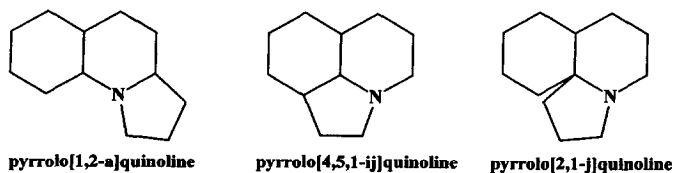
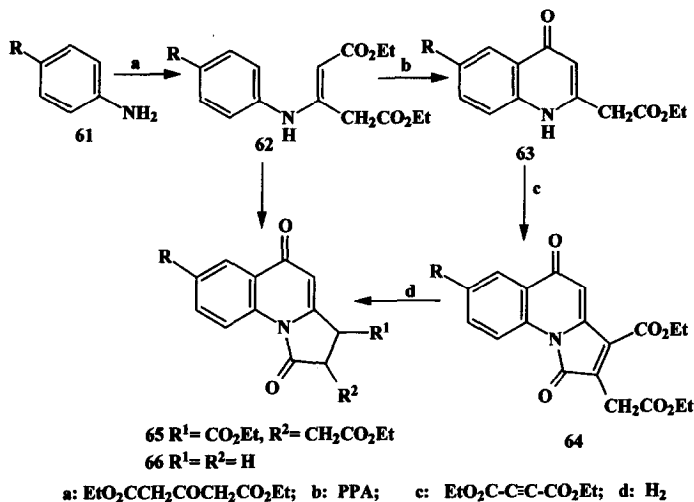


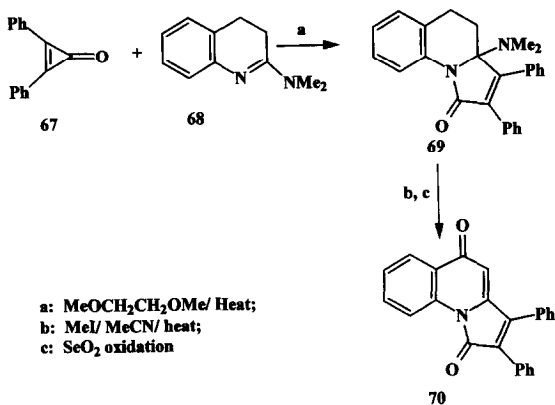
Fig. 4



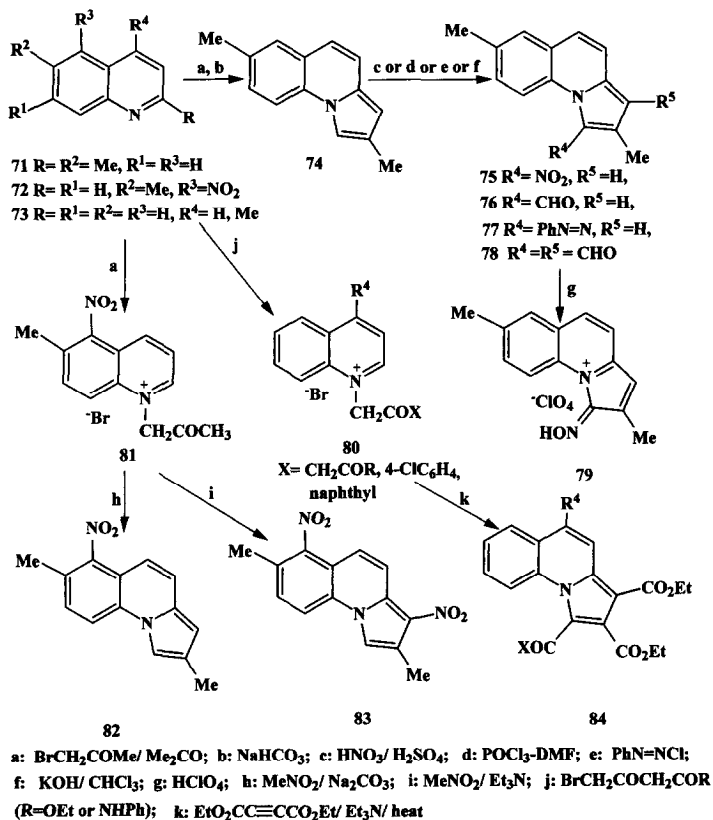
Scheme 12

with MeI followed by oxidation gave the pyrroloquinoline **70** (85S619) (Scheme 13).

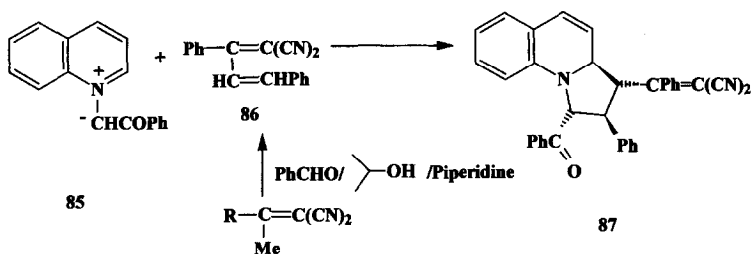
Tschitschibabin reaction on quinoline derivative **71** with bromoacetone and subsequent treatment with base afforded the pyrrolo[1,2-*a*]quinoline **74**. Nitration of **74** with nitric acid in acetic acid containing a trace amount of sulfuric acid gave the 1-nitro derivative **75**. Formylation of **74** through Vilsmeier–Haack reaction afforded the 1-formyl derivative **76**. Coupling of a diazonium salt with **74** gave the 1-diazo derivative **77**. Reimer Tiemann formylation of **74** afforded the 1,3-diformyl derivative **78**. Treatment of **75** with perchloric acid gave **79**. Reaction of **72** with bromoacetone gave **81** which upon treatment with nitromethane and sodium carbonate gave **82**, whereas replacing the carbonate by triethylamine gave the nitro derivative **83** (79JHC393). Reaction of the quinoline **73** with 4-bromoacetoacetic acid derivatives or phenacyl bromide gave the corresponding dioxobutylide or phenacyl derivatives **80** that were cyclized with diethyl acetylenedicarboxylate to afford **84** (77CPB203, 83JCED283, 96IJC(B)1329) (Scheme 14).



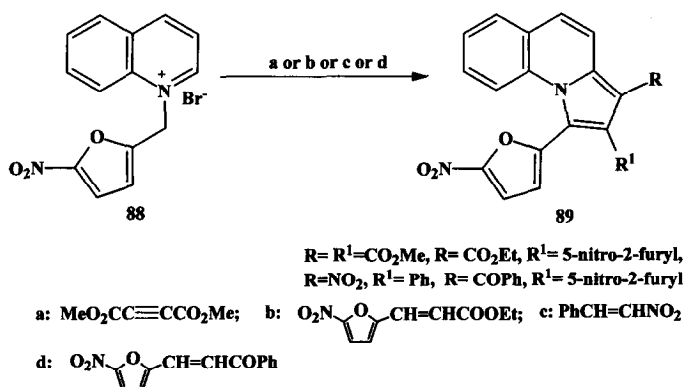
Scheme 13



Scheme 14



Scheme 15



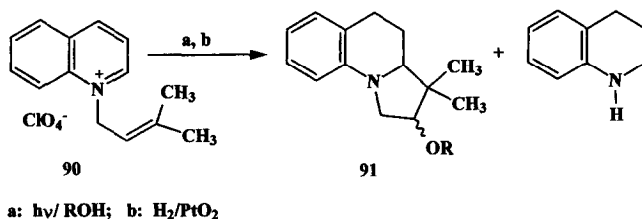
Scheme 16

The 1,3-dipolar cycloaddition of dienes **86** with phenacyl derivatives **85** gave the pyrrolo[1,2-*a*]quinoline **87** regio- and stereoselectively (90DOK1156) (Scheme 15).

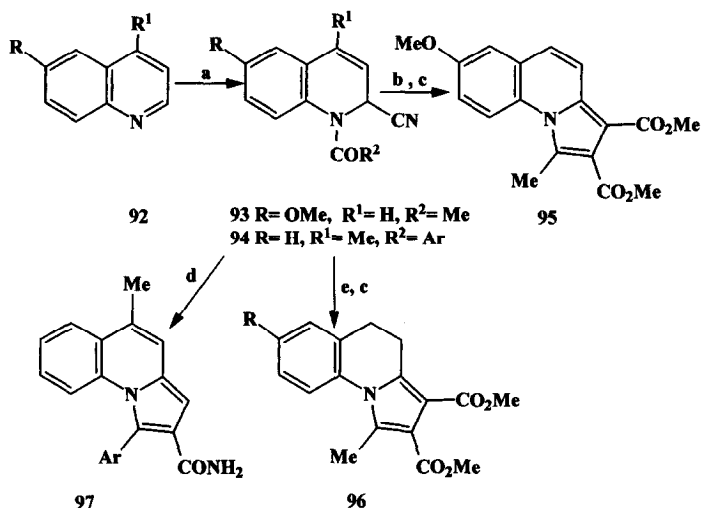
Cycloaddition of 4-nitrofurylmethylquinolinium bromide **88** with dimethyl acetylenedicarboxylate, nitrostyrene, ethyl 3-(5-nitro-2-furyl)-2-propenoate and 1-phenyl-3-(5-nitro-2-furyl)-2-propenone afforded the corresponding furylbenzoindolizine **89** (86CCC412) (Scheme 16).

Electron transfer initiated photocyclization of a methanolic solution of **90** followed by catalytic hydrogenation gave a mixture of benzoindolizines **91** and tetrahydroquinoline. Hydrogenation is necessary to stabilize one of the proposed products (82TL919, 83JA1204) (Scheme 17).

The Reiser compound **93**, prepared from quinoline derivatives **92**, gave upon reaction with dimethyl acetylenedicarboxylate the pyrroloquinoline **95**. Reduction of **93** gave the tetrahydro derivative that upon reaction with dimethyl acetylenedicarboxylate afforded **96** (85JOC722). Reaction of **94** with acrylonitrile in presence of base gave pyrroloquinoline **97** (77JCS(P1)2018) (Scheme 18).



Scheme 17



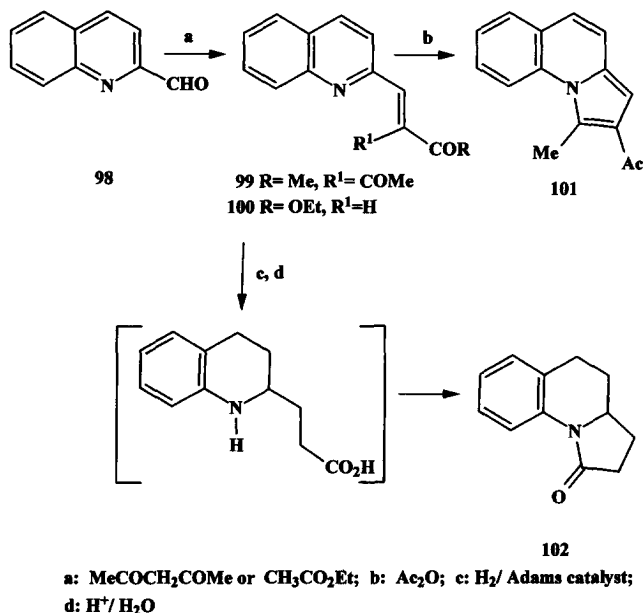
a: R<sup>2</sup>C(OMe)/Me<sub>3</sub>SiCN/AlCl<sub>3</sub>; b: HBF<sub>4</sub>/AcOH or CF<sub>3</sub>SO<sub>3</sub>H/CH<sub>2</sub>Cl<sub>2</sub>;  
c: MeO<sub>2</sub>C-C≡C-CO<sub>2</sub>Me; d: NaH/DMF/CH<sub>2</sub>=CHCN; e: H<sub>2</sub>/Pd-CaCO<sub>3</sub>

Scheme 18

Condensation of 2-quinolinecarboxaldehyde **98** with acetylacetone or ethyl acetate gave the acrylate derivatives **99** and **100**, respectively. Cyclization of **99** with Ac<sub>2</sub>O afforded the benzindolizine **101** (80ACSA(B)79). Reduction of **100** in presence of Adams catalyst followed by hydrolysis gave **102** (78PJC107) (Scheme 19).

Reaction of methyl 2-quinolylacetate with 2-*N*-trifluoroacetyl-amino-5-bromo-4-oxonorvaline methyl ester gave **103**, a tryptophan analogue of pyrroloquinoline (96KG1510).

Hydroxyethylation of 2,6-dimethylquinoline with ethylene oxide in presence of Li in PhBr gave **104** which was hydrogenated to the tetrahydro derivative **105**. Its cyclization with P<sub>2</sub>O<sub>5</sub>/xylene gave the pyrroloquinoline **106**. Nitration of **106** with fuming HNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub> afforded a mixture



Scheme 19

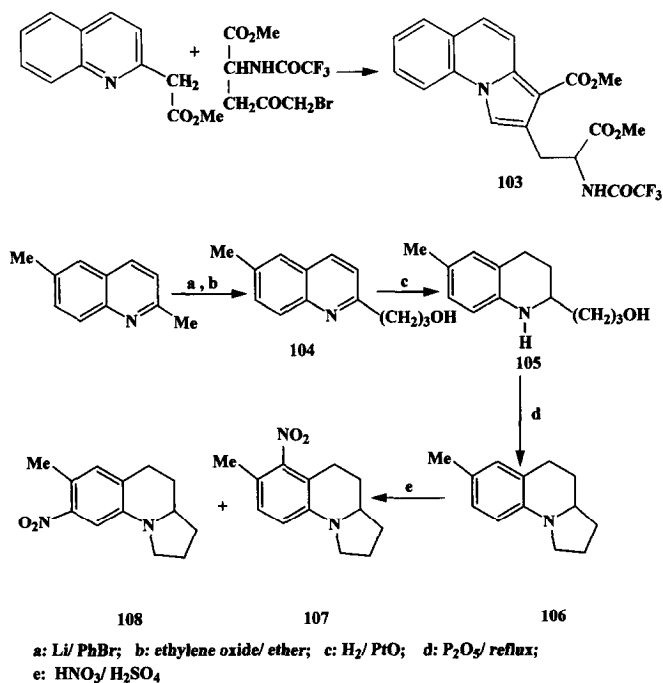
of 6- and 8-nitropyrroloquinolines **107** and **108**, respectively (78MI77) (Scheme 20).

Thermal rearrangement of 4-allyloxy-2-methylquinolines gave **109** whose annulation with NBS in  $\text{CCl}_4$  gave the pyrrolo[1,2-*a*]quinoline **110** which upon dehydrobromination gave **111** functionalized with an exo methylene group on the fused ring (92JOC6991). Alternatively, thermolysis of the corresponding 4-propargyloxyquinoline gave **111** (Scheme 21).

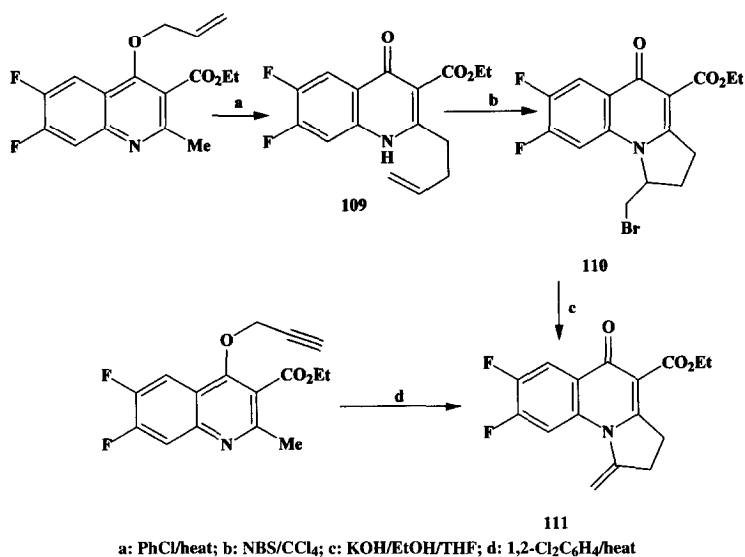
Reaction of anthranilic acid **112** with acid anhydrides afforded the corresponding imide derivatives **113**. Subjecting **113** to intramolecular Wittig cyclization has been achieved by treatment with *N*-phenyl(triphenylphosphoranylidene)etheneimine in toluene or dioxane whereby the corresponding pyrroloquinolines **116** were obtained (94TL9229). The intermediate **115** resulting from the rearrangement of **114** could be isolated when the reaction was done at room temperature (Scheme 22).

Condensation of *o*-aminoacetophenone with maleic, succinic or phthalic anhydrides gave **117** whose bromination with  $\text{CuBr}_2$  gave the bromides **118**. Column chromatographic separation of the respective maleimide derivative on silica gel gave the bromoquinoline **119** whereas the phthalimide derivative was obtained from **118** by cyclization with  $\text{Et}_3\text{N}$  (93MI11). On the

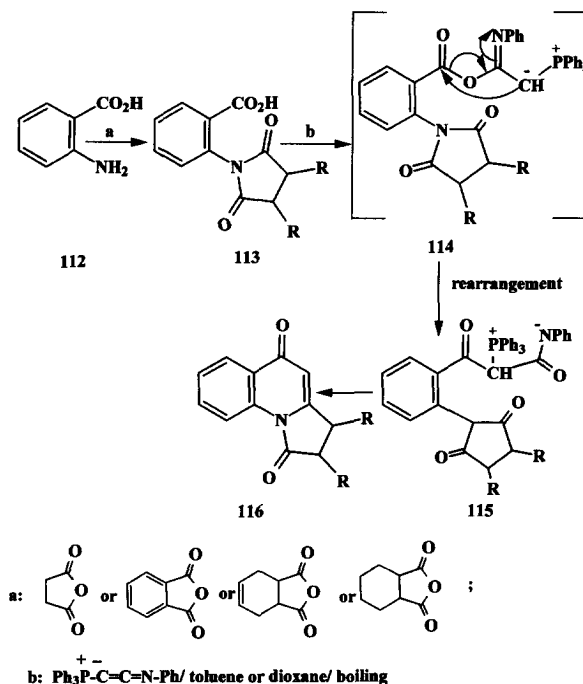




Scheme 20



Scheme 21

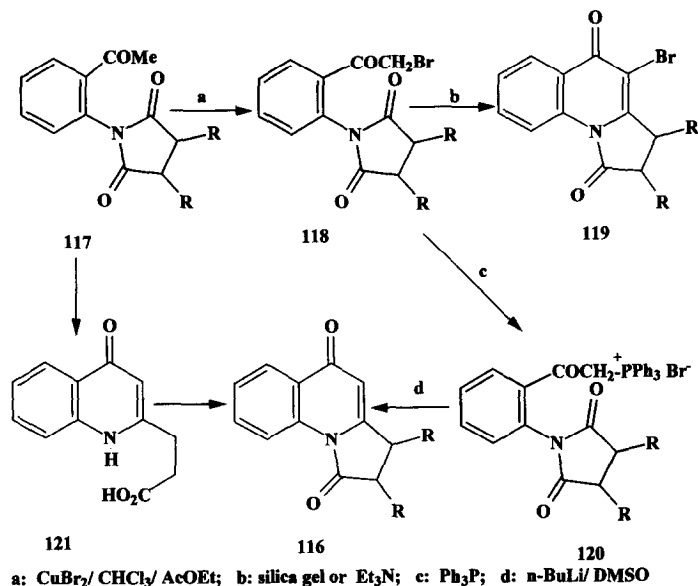


Scheme 22

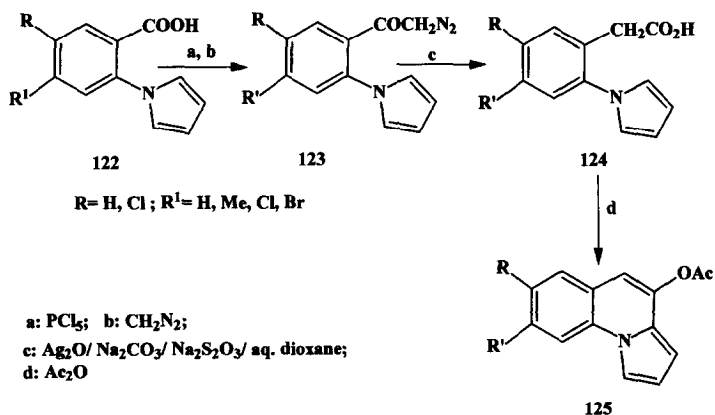
other hand, reaction of **118** with  $\text{Ph}_3\text{P}$  gave **120** whose cyclization to **116** was effected with  $n\text{-BuLi}$  in DMSO (92SC2659). The pyrroloquinolines resulted along with the respective imides upon reaction of *o*-aminoacetophenones with anhydrides (92JCR(S)260). Cyclodehydration of the imide **117** gave **121** which could be transformed to **116** (97H1979) (Scheme 23).

Reaction of 2-pyrrolylbenzoic acid derivative **122** with  $\text{PCl}_5$  and subsequent reaction with diazomethane gave the diazoacetophenone **123** that upon treatment with silver oxide, sodium carbonate and sodium thio-sulfate afforded acetic acid derivative **124**, cyclization with acetic anhydride gave **125** (91JHC77) (Scheme 24).

Reaction of aniline derivatives with 4-chlorobutyroyl chloride followed by cyclization with sodium ethoxide and subsequent thionation promoted by sonication gave the corresponding *N*-arylpyrrolidine-2-thiones **126**. Zinc-mediated condensation of diethyl bromomalonate with **126** using iodine as activator gave the vinylogous urethanes **127** whose cyclization with PPA gave the tricyclic compound **128** which upon hydrolysis afforded the acid **129** (96TL9403).



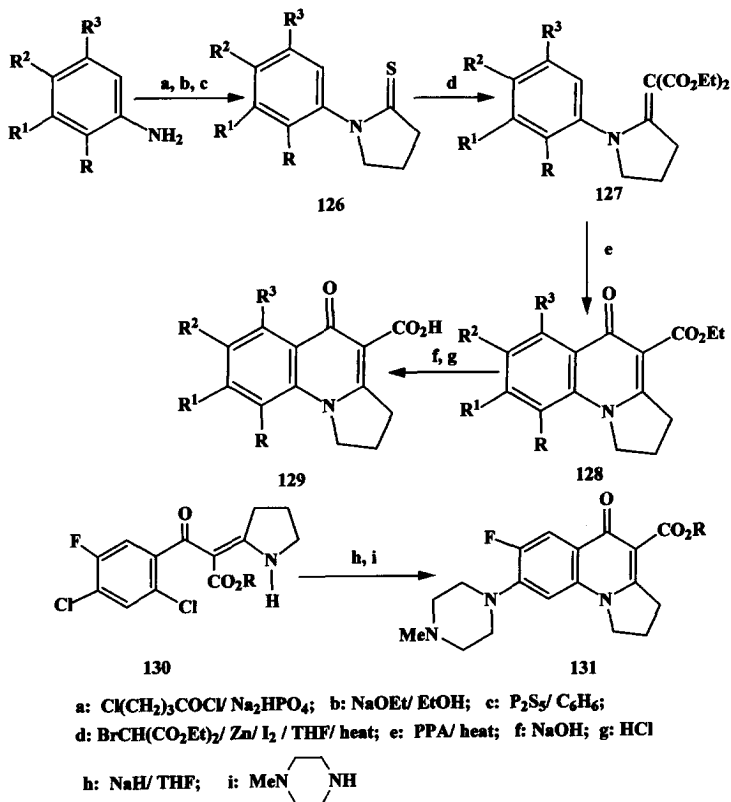
Scheme 23



Scheme 24

Treatment of the pyrrolidine derivative **130** with sodium hydride followed by *N*-methyl piperazine afforded pyrrolidino[1,2-*a*]quinolinone 4-carboxylate **131** (93JPR397) (Scheme 25).

Reaction of the chloro-substituted propargyl acetate **132** with aniline gave the pyrrolidine derivative **133** that was cyclized through treatment with

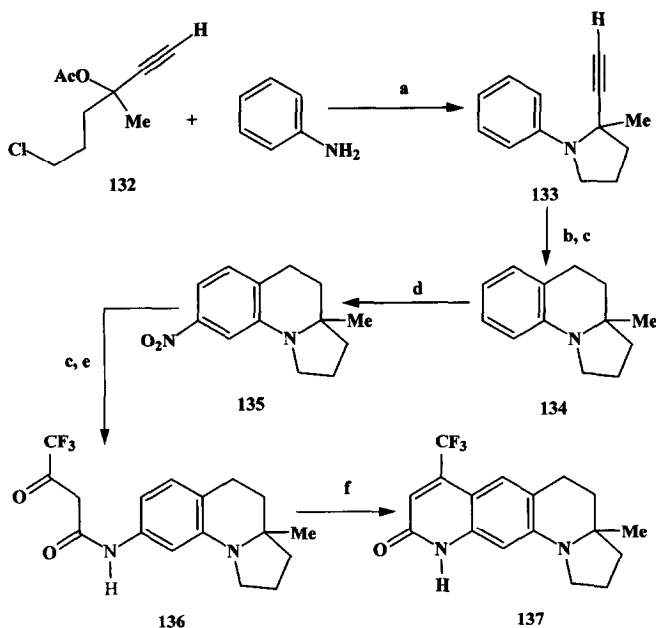


Scheme 25

$\text{CuCl}/\text{THF}$  followed by catalytic hydrogenation to give the pyrroloquinoline **134**. Nitration of the later gave the 9-nitro derivative **135**. Reduction of **135** followed by reaction with ethyl trifluoroacetoacetate gave **136** that upon cyclization gave the tetracyclic compound **137** (98JMC623) (Scheme 26).

Thermal cyclization of 2-vinyl-*N,N*-dialkylanilines **138** afforded **139** with creation of a new chiral center in 98% purity (89JOC199). In case of pyrrolidine with methyl or methoxymethyl substituent, cyclization with  $\text{ZnCl}_2$  occurs via an irreversible 1,5-hydrogen shift in boiling acetonitrile (87JA3136) or  $\text{BuOH}$  (91RTC115) to afford the diastereoisomers **140** (33%), **141** (35%) and **142** (6%) (87JA3136) (Scheme 27).

Thermolysis of the azido derivative **143** ( $\text{R} = \text{R}^1 = \text{H}$ ) in refluxing 1,2-dichlorobenzene gave the pyrroloquinoline **144** and the dihydropyrrolo derivative **145** amongst other products (79H1021), whereas its thermal



a:  $\text{CuCl}/\text{NEt}_3/\text{THF}$ ; b:  $\text{CuCl}/\text{THF}$ ; c:  $\text{H}_2/\text{Pd-C}$ ; d:  $\text{HNO}_3/\text{H}_2\text{SO}_4$ ;  
e:  $\text{F}_3\text{CCOCH}_2\text{CO}_2\text{Et}$ ; f:  $\text{ZnCl}_2/\text{benzene}$

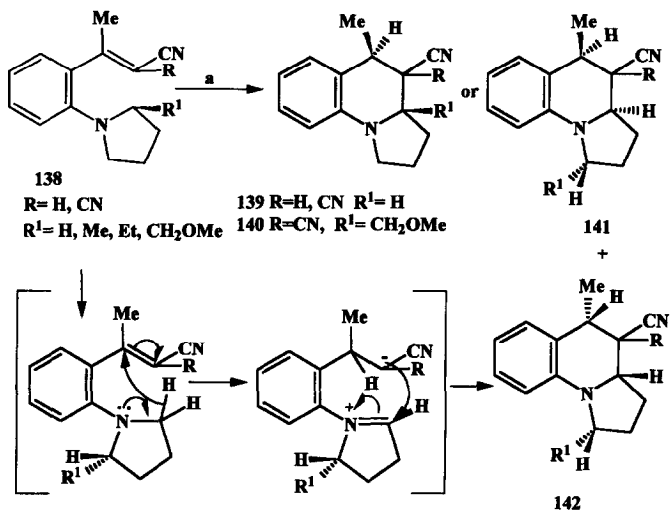
Scheme 26

decomposition gave only **145** (82CPB140). On the other hand, thermolysis of **143** ( $\text{R} = \text{R}^1 = \text{OMe}$ ,  $\text{RR}^1 = \text{OCH}_2\text{O}$ ) gave **144** (82CPB140). Photolysis of **143** ( $\text{R} = \text{R}^1 = \text{H}$ ) in ethanol gave 1-ethoxypyrroloquinoline derivative **146** (79H1021) (Scheme 28).

Reaction of the allylborane **147** with **148** then workup with  $\text{KOH}$  gave the *E* isomer, while the workup with sulfuric acid gave the *Z* isomer **149**. Heating the azidodiene **149** in  $\text{CDCl}_3$  in a sealed tube afforded **150** in one step. The stereoselectivity of the reaction was found to be slightly dependent on the geometry of the diene (89TL6661) (Scheme 29).

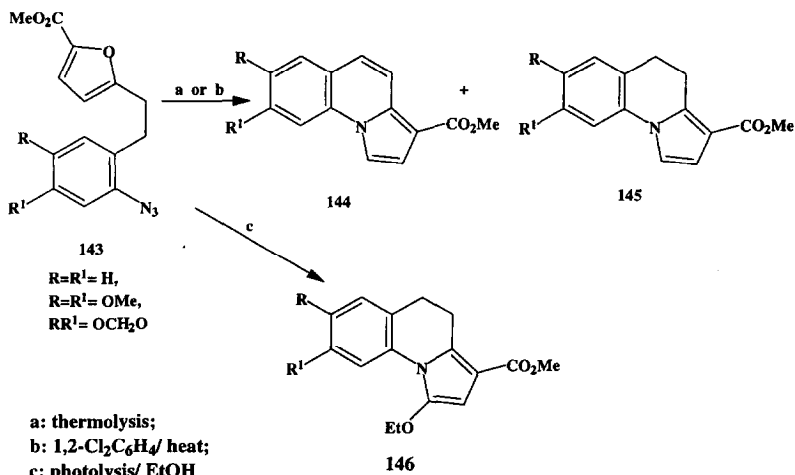
Cyclocondensation of the amine **151** with the ketoester **152** gave **153** that can be selectively alkylated to give **154** which upon benzylation and alkylation gave **155** as central nervous system agent (83EP90516) (Scheme 30).

Cyclocondensation of **156** with bromoethylpyrrolidine **157** gave the *trans*-enamine **158** which upon reduction gave (+) gephyran **159** in 40% yield and a small amount of isomer **160** (80N193) (Scheme 31).



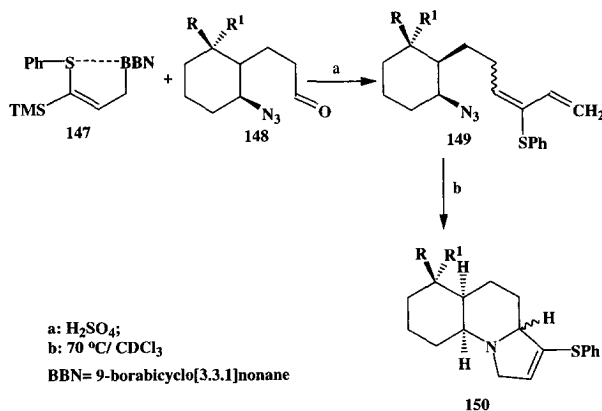
a: ZnCl<sub>2</sub>/ MeCN/ reflux; or BuOH/ reflux

Scheme 27

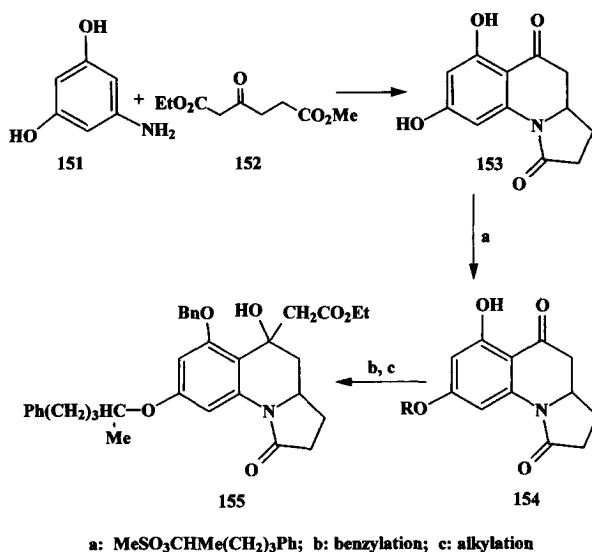


Scheme 28

A total synthesis of (+/-)-gephyrotoxin started with the pyrrolidine-2,4-dione **161** which upon treatment with ethoxyacetylene magnesium chloride followed by dilute HCl gave the acrylate derivative **162**. Subsequent reduction and treatment with phenoxyformyl chloride afforded **163**.

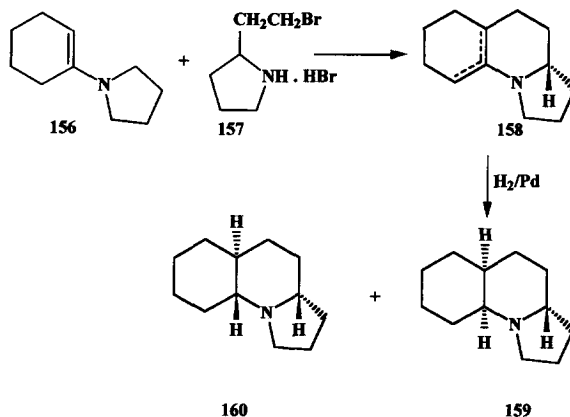


Scheme 29



Scheme 30

Reduction with  $\text{LiBH}_4$  followed by treatment with  $\text{KH}$ ,  $\text{BnBr}$  followed by  $\text{N}$ -deprotection with  $\text{Ba}(\text{OH})_2$  to give **164** which upon reaction with cyclohexane-1,3-dione gave **165**. Reaction of **165** with  $\text{MeSCl}$  followed by  $\text{LiBr}$  then reduction with  $\text{H}_2$ ,  $\text{Pd/C}$  gave **166**. The products from reduction of **166** depend upon the reaction condition. Thus, hydrogenation of **166** under pressure gave **167** together with the reduced product **168**. On the other hand, when the reaction catalyst was  $\text{Pt}$ -alumina the stereochemical configuration was reversed to give **169** (80JA7154) (Scheme 32).



Scheme 31

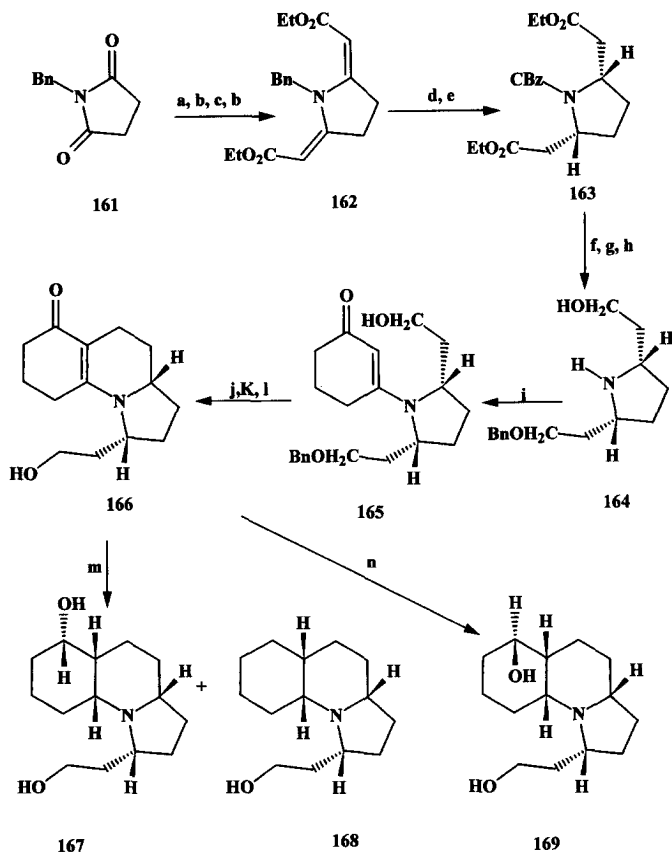
The assignment of the absolute configuration of gephyrotoxin led to its synthesis in the optically active form (81TL4197). Thus, treating the optically active pyrrolidinone nitrile **170** with  $P_2S_5$  followed by ethyl bromoacetoacetate then KOH gave the ester **171** that was hydrogenated to afford a mixture of **172** and **173**. Reaction of **172** with  $PhOCOCl$  followed by reduction with  $LiBH_4$  and subsequent treatment with bromoacetone afforded the pyrroxazinone **174**. Conversion of **174** to **175** was carried out by treatment with DIBAL followed by 3 N HCl, reduction with  $NaBH_4$ , alkylation with bromoacetone and then  $Ba(OH)_2$  (81TL4197). Construction of the fused ring in **175** was carried out as in the former scheme (80JA7154) (Scheme 33).

1,3-Cycloaddition of nitrones **176** with methylenecyclopropane **177** in toluene afforded two regioisomers **178** and **179**. Heating **179** in toluene gave the pyrrolo[1,2-*a*]quinoline **180** (92JOC5666). On the other hand, thermal rearrangement of isoxazoline-5-spirocyclopropanes **181** in anhydrous DMF containing  $K_2CO_3$  gave **183** and boiling **182** in anhydrous mesitylene gave **184** (92JOC4206) (Scheme 34).

Reaction of 2-methoxytetrahydropyrrole with dioxalane-2,4-dione in presence of  $Et_3N$  in benzene followed by treatment with MeONa in methanol afforded the monocyclic intermediate **185**. Its treatment with BuLi followed by perfluorobenzoyl chloride gave **186** whose hydrolysis gave **187** which possess low or no antibacterial activity (96PHA805). Regiospecific intramolecular cyclization of **188** with sodium hydride yielded **189** as ester whose hydrolysis gave the respective acid (87JHC1537) (Scheme 35).

Flash vacuum pyrolysis of alkenylbenzoxazine **190** gave **192** whose low yield was attributed to the competition between H-shift and intramolecular cycloaddition in the intermediate **191** (82TL4501) (Scheme 36).



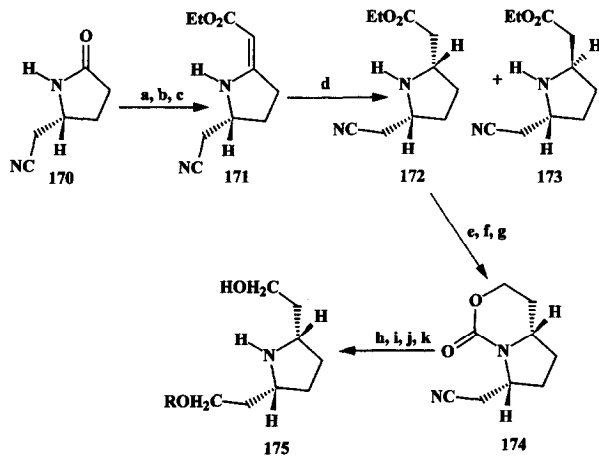


a:  $\text{EtOC}\equiv\text{CMgCl}/\text{THF}$ ; b: 5%  $\text{HCl}$ ; c:  $\text{EtOC}\equiv\text{CMgBr}/\text{THF}$ ; d:  $\text{H}_2/\text{Pd-C}/\text{HClO}_4/\text{MeOH}$ ; e:  $\text{PhOCOCl}/\text{Py}/\text{CH}_2\text{Cl}_2$ ; f:  $\text{LiBH}_4/\text{THF}$ ; g:  $\text{KH}/\text{THF}$ ; h:  $\text{Bn Br}/\text{DMF}$ ; i: cyclohexane-1, 3-dione/py-Tos-OH/ $\text{C}_6\text{H}_6$ ; j:  $\text{MeSCl}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ ; k:  $\text{LiBr}/\text{DMF}$ ; l:  $\text{H}_2/\text{Pd-C}/\text{HClO}_4$ ; m:  $\text{H}_2/\text{Pd-C}$  (10%)/ $\text{AcOEt}$ ; n:  $\text{H}_2/\text{Pt-Alumina}/\text{AcOEt}$

Scheme 32

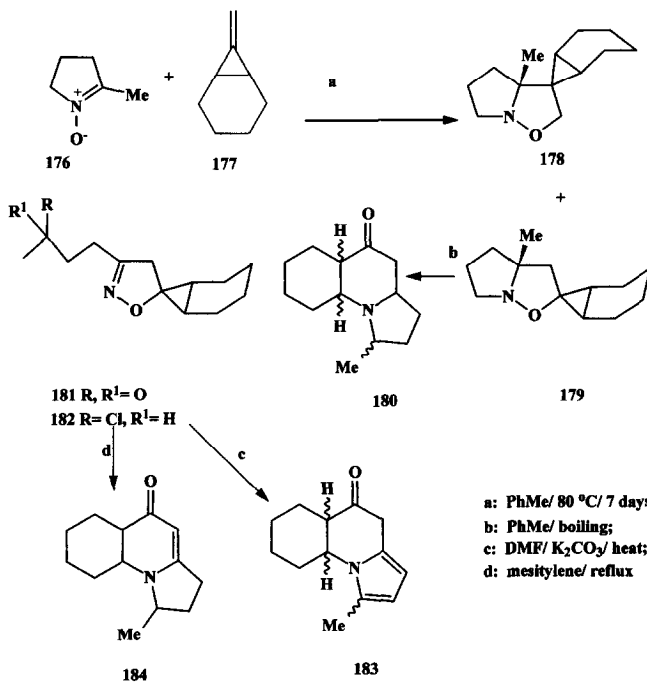
## 2. Pyrrolo[4,5,1-ij]quinolines

Several pyrrolo and indoloquinolines of this class of ring system were prepared via the Fischer indole synthesis (78KG200). Reaction of tetrahydroquinoline **193** with methyl trifluoropyruvate gave the acenaphthene analogue **195** (86IZV2074). Similarly, **196** was prepared (89IZV472). On the other hand, condensation of **194** with chloroacetyl chloride afforded **197** whose condensation with nitrosodimethylaniline gave **199** which could be cyclized with acid to give pyrroloquinoline dione **200** (86USP4593092). Alternatively, reaction of **194** with oxalyl chloride followed by cyclization



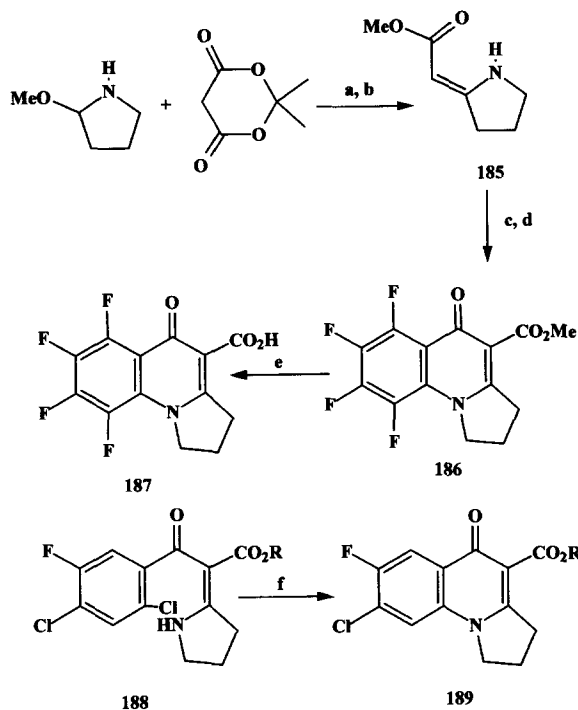
a:  $P_2S_5/Py/80^\circ C$ ; b:  $MeCOCHBrCO_2Et$ ; c:  $0.1\ N\ KOH/EtOH/60^\circ C$ ;  
d:  $H_2/Pt-C/HClO_4/MeOH/rt$ ; e:  $PhOCOC/Py/CH_2Cl_2/rt$ ; f:  $LiBH_4/THF$ ;  
g:  $MeOCH_2Br/rt$ ; h:  $DIBAL/THF/PhMe$ , then  $3N\ HCl$ ; i:  $NaBH_4/DME/rt$ ;  
j:  $MeOCH_2Br/EtN(i-Pr)_2/CH_2Cl_2/rt$ ; k:  $Ba(OH)_2/H_2O/reflux$

Scheme 33

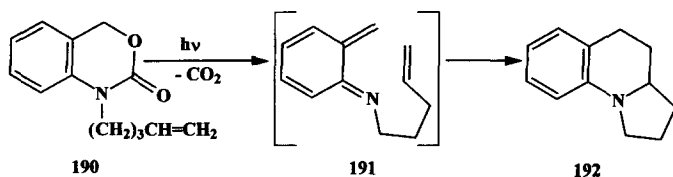


a:  $PhMe/80^\circ C/7\ days$ ;  
b:  $PhMe/boiling$ ;  
c:  $DMF/K_2CO_3/heat$ ;  
d:  $mesitylene/reflux$

Scheme 34



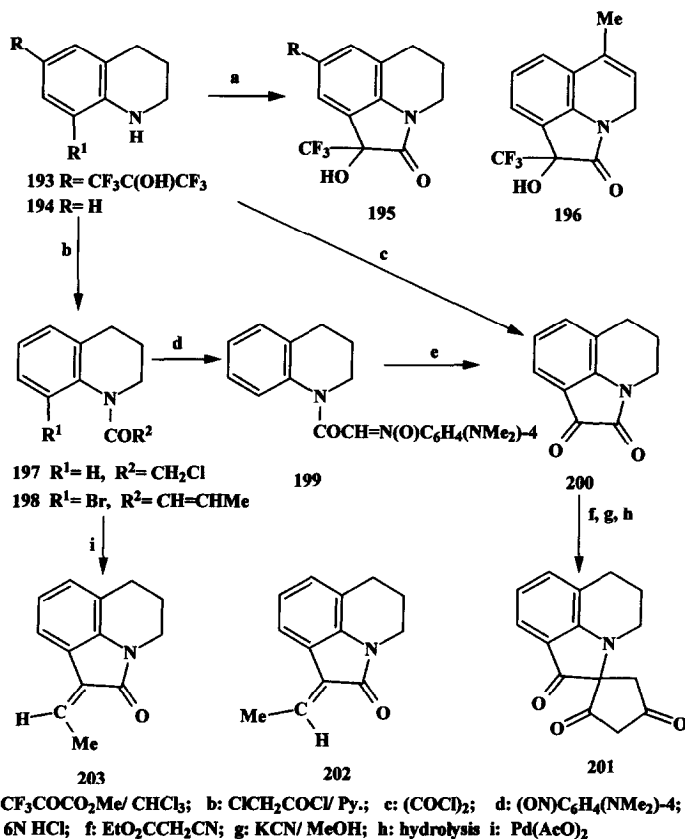
Scheme 35



Scheme 36

afforded **200** which was found to be an effective inhibitor of aldose reductase (79USP4151282). Methylenation of **200** with ethyl cyanoacetate and subsequent cyclocondensation with potassium cyanide in methanol followed by hydrolysis and decarboxylation gave the spiro compound **201** (86USP4593092). Cyclization of **198** using  $\text{Pd}(\text{AcO})_2$  gave a mixture of the pyrroloquinolines **202** and **203** (95JOC2312) (Scheme 37).

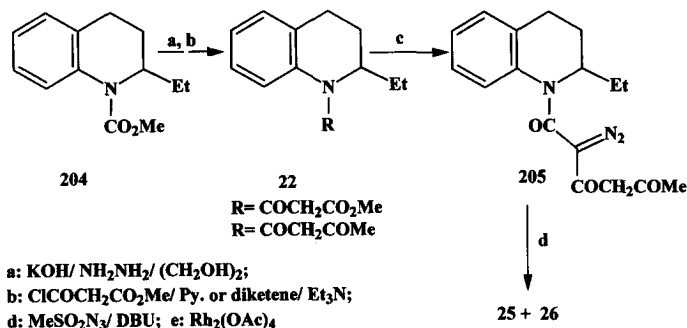
Decarbamoylation and acylation of **204** which was prepared by catalytic hydrogenation of the corresponding carbamate (71BCJ520) afforded **22**. A diazotransfer reaction upon treatment of **22** ( $\text{R} = \text{CO}_2\text{Me}$  or  $\text{COMe}$ ) with



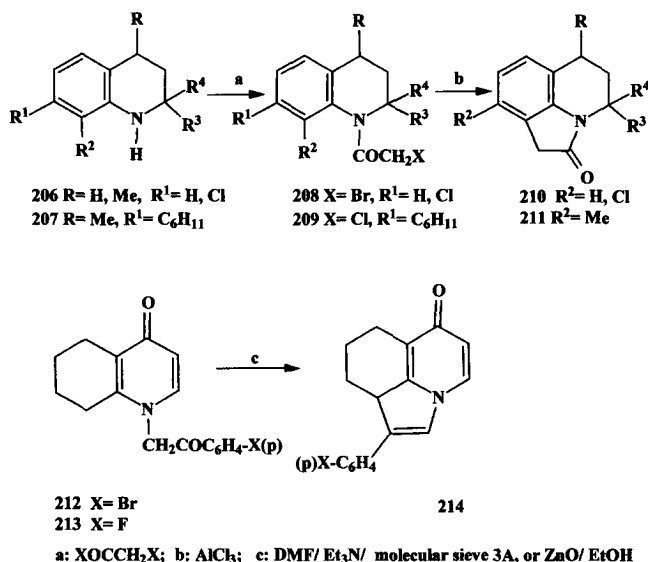
Scheme 37

methylsulfonyl azide gave the respective diazo amides **205**. Treatment of the acetyl derivative **205** with  $Rh_2(OAc)_4$  afforded the pyrroloquinoline **26** as the major product (88%) in addition to the azetidinone **25** (2%). On the other hand, the ester derivative gave a mixture of diastereoisomers of the azetidinone **25** (85%) as major product suggesting a subsequent effect of the substituent on the chemoselectivity of the C–H insertion reaction (92JOC4404) (Scheme 38).

Treating tetrahydroquinoline derivatives **206** with bromoacetyl bromide gave the 1-bromoacetyl derivatives **208** which upon cyclization with  $AlCl_3$  afforded the pyrroloquinolines **210** as tranquilizers and sedatives (77USP4015005). A similar reaction of **207** with chloroacetyl chloride gave **209**, that upon treatment with  $AlCl_3$  led to a cleavage of the cyclohexyl group, cyclization and migration of the methyl group from position 8 to 7 to



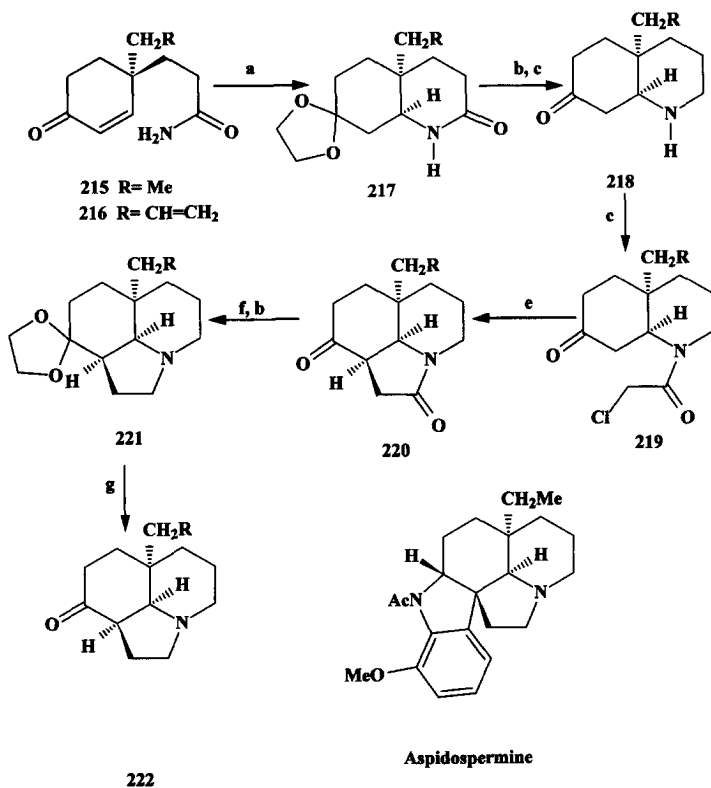
Scheme 38



Scheme 39

give the pyrroloquinoline **211** (77MI104). Analogues of **211** having a spiro ring at C-8 were similarly prepared (99JHC675) from the spiro derivatives of **206** (89KG1514, 91KG947). Reaction of 5,6,7,8-tetrahydroquinolin-4-one with 4-halophenacyl bromides gave **212** and **213** that was cyclized by heating in DMF/ $\text{Et}_3\text{N}$  and molecular sieves to give **214** where the 4-bromoderivative showed antiallergic effect (93WOP9322313). The respective 4-fluoro analogue was obtained using  $\text{ZnO}_2$  in ethanol as cyclizing agent (91EP414023) and showed 3-hydroxy-3-methylglutaryl-CoA reductase inhibition (91EP414023) (Scheme 39).

The 1,2,5,6-tetrahydropyrrolo[3,2,1-*ij*]quinoline is the basic skeleton of lilolidine (71CPB832) and the aspidospermine alkaloids. The racemic form of aspidospermine was prepared by Fischer indole synthesis on racemic form of **222** (63JA2872, 65TL2261, 77T1641) as a precursor for aspidospermine (89JOC4673). Thus, cyclization of the cyclohexenone derivative **215** by heating in benzene with catalytic amount of *p*-toluenesulfonic acid and then with ethylene glycol and heating gave **217** in a single isomeric form as a result of acid-catalyzed equilibration. Subsequent reduction with  $\text{LiAlH}_4$  and hydrolysis of the ketal group gave **218** (89JOC4673). Chloroacetylation of **218** afforded the corresponding chloroacetyl derivative **219** which upon cyclization with  $\text{tBuOK}/\text{C}_6\text{H}_6$  gave **220** that upon ketalization afforded **221**. Reduction of **221** according to Stork method afforded the chiral hydroxilolidine **222** (Scheme 40).



Scheme 40

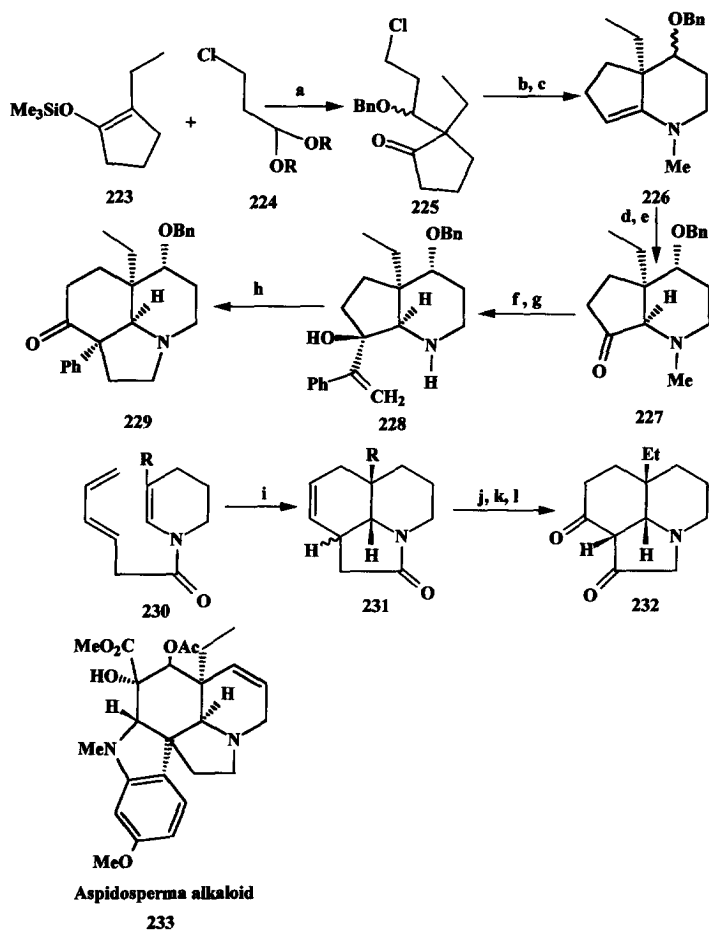
Stereoselective assembly of the hydrolilolidine derivative **229** as intermediate in the synthesis of aspidosperma alkaloid **233** was carried out through alkylation of the trimethylsilyl enol ether **223** with 3-chloropropionaldehyde dibenzyl acetal **224** to give the corresponding cyclopentanone **225**. Displacement of the chloride with NaI in 2-butanone gave the iodo derivative which upon treatment with methyl amine in presence of  $\text{MgSO}_4$  gave the bicyclic enamine **226**. Hydroboration, oxidation (67JOC4157) and subsequent epimerization of **226** gave the ketone **227**. Reaction of **227** with 1-phenylvinyl lithium followed by phenyl chloroformate and N-demethylation gave **228**. Treatment with paraformaldehyde and D-10-camphorsulfonic acid gave the hydrolilolidine **229** (81T4041). On the other hand, the analogue **232** could be synthesized by cyclization of the enamidodiene **230** by thermolysis to afford **231**. Treatment with  $\text{SeO}_2$  followed by aqueous KOH then  $\text{H}_2\text{CrO}_4$  gave the ketolactam **232** (80JA3294) (Scheme 41).

Cyclization of the salt **234** with sodium hydrogen carbonate gave pyrroloquinoline **235** (82JOC688, 85JHC1049) which upon reaction with acetylene derivatives afforded the tetracyclic benzocyclazine **236**. Cyclization of **235** with dibenzoyl acetylene gave **237** which upon reaction with hydrazine gave the pyridazine **238** (85JHC1049) (Scheme 42).

Cyclization of the bromide **239** with NaOEt gave **240** whereas reaction of **239** with base and vinylating, alkylating or acylating agents afforded 1-vinylpyrroloquinolines **241** (86CPB2435) which could be transformed into furo or pyranopyrroloquinolines. Some of the compounds showed antiallergic activity (Scheme 43).

Allylation of the 7-hydroxyquinoline derivative **242** with allyl bromide gave the corresponding 7-allyl ether **243** which underwent Claisen rearrangement to give the 8-allyl derivative **244**. Acylation and subsequent bromination afforded the dibromopropyl derivative **245**. Treatment of **245** with KOH/EtOH gave 8-hydroxypyrroloquinoline **246** that was methylated with methyl iodide to afford **247** (91JOC980) (Scheme 44).

Reduction of quinoline **248** with  $\text{NaCNBH}_3/\text{AcOH}$  afforded the corresponding tetrahydroquinoline **249** which upon nitrosation followed by reduction with  $\text{LiAlH}_4$  afforded 1-aminoquinoline **250** that was reacted with ethyl levulinate to give the pyrroloquinoline derivative **251** (95JMC669). Reduction of the ester **251** with  $\text{LiAlH}_4$  gave the corresponding alcohol that was brominated with  $\text{PBr}_3$  to the bromoethyl derivative **255**. Condensation of **255** with a piperazine derivative afforded **254** as drugs (93GEP4128015, 95JMC669). Hydrolysis of **251** gave the corresponding acid which upon treatment with the piperazine derivative afforded **256**. Reaction of **249** with phenylacetone gave **252** that upon reaction with oxalyl chloride followed by substituted piperazine afforded **253** (95JMC669). Structure-activity relationship studies showed that the optimum biological activity depend



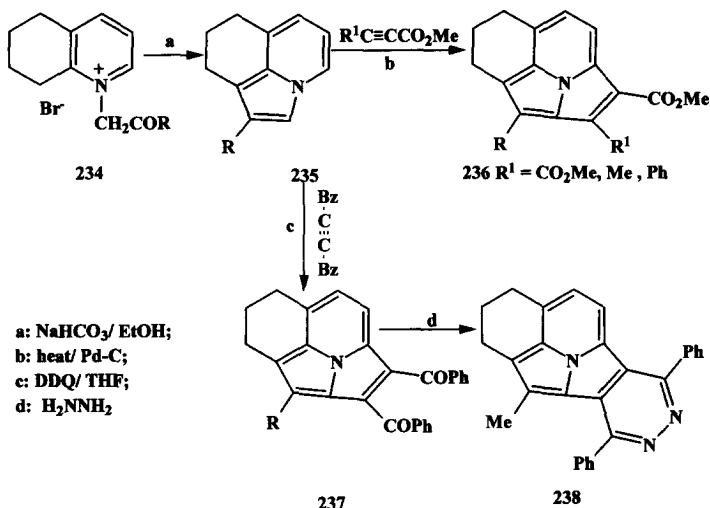
a:  $\text{TiCl}_4$ ; b:  $\text{NaI}/\text{MeCOEt}$ ; c:  $\text{MeNH}_2/\text{MgSO}_4$ ; d:  $\text{BF}_3\cdot\text{OEt}_2/\text{LiAlH}_4$ ;  
e:  $\text{DMSO}/(\text{COCl})_2/\text{NaOMe}$ ; f:  $\text{PhCH}=\text{CH}_2$ ; g:  $\text{ClCO}_2\text{Ph}$ ; h:  $(\text{CH}_2\text{O})_n$ /  
d-10-camphorsulphonic acid; i: Thermolysis; j:  $\text{SeO}_2/\text{AcOH}$ ; k:  $\text{KOH}/$   
 $\text{EtOH}/\text{H}_2\text{O}$ ; l:  $\text{H}_2\text{CrO}_4/\text{Py}/\text{CH}_2\text{Cl}_2$

Scheme 41

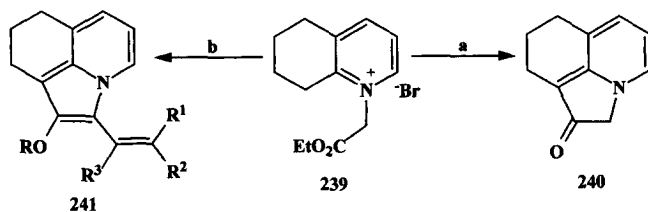
upon the presence of 4-methylpyridine-2-yl-piperazine moiety on the 1-position for potent antiasmatic and antihistamine activities as well as *in vitro* PAF antagonism (95JMC669) (Scheme 45).

Reaction of tetrahydroquinoline **257** with ethyl bromopyruvate afforded pyrroloquinoline **260** which upon transesterification by treatment with tropine in presence of sodium methoxide in toluene gave **261** which was found to be useful as 5-HT receptor antagonist (89EP322016).





Scheme 42



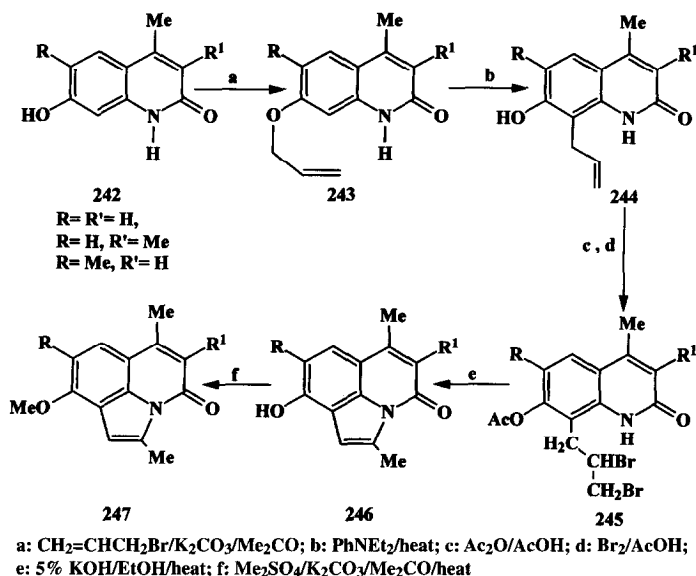
**a:** NaOEt/ EtOH; **b:** heating with base/ alkylation or acylation

Scheme 43

Intramolecular cyclocondensation of *N*-acetylaminoquinoline **258** by treatment with POCl<sub>3</sub> afforded the pyrroloquinoline **262** (90KG337). Treatment of **257** with COCl<sub>2</sub>/THF and the product was heated under reflux with CS<sub>2</sub> and AlCl<sub>3</sub> (90EP403980) to afford the dioxopyrroloquinoline **259** that upon oxidation with H<sub>2</sub>O<sub>2</sub> in aqueous NaOH afforded **263** (90EP403980) (Scheme 46).

Reaction of **264** with 1-chloro-4-phenoxybut-2-yne in the presence of K<sub>2</sub>CO<sub>3</sub> gave **265**. Oxidation of the latter with *m*-chloroperbenzoic acid gave the dimer **266**. On the other hand, carrying the oxidation in presence of KCN afforded a mixture of **266** and **267** (87JCS(CC)524) (Scheme 47).

Treatment of 4-arylamino-8-iodoquinoline **268** with propargyl alcohol in presence of iodo(phenyl)bis(triphenylphosphine) palladium and copper (I)iodide afforded **269** which upon catalytic reduction using Linder's catalyst gave 4*H*-pyrrolo[3,2,1-*ij*]quinoline **270** (97H2395) (Scheme 48).

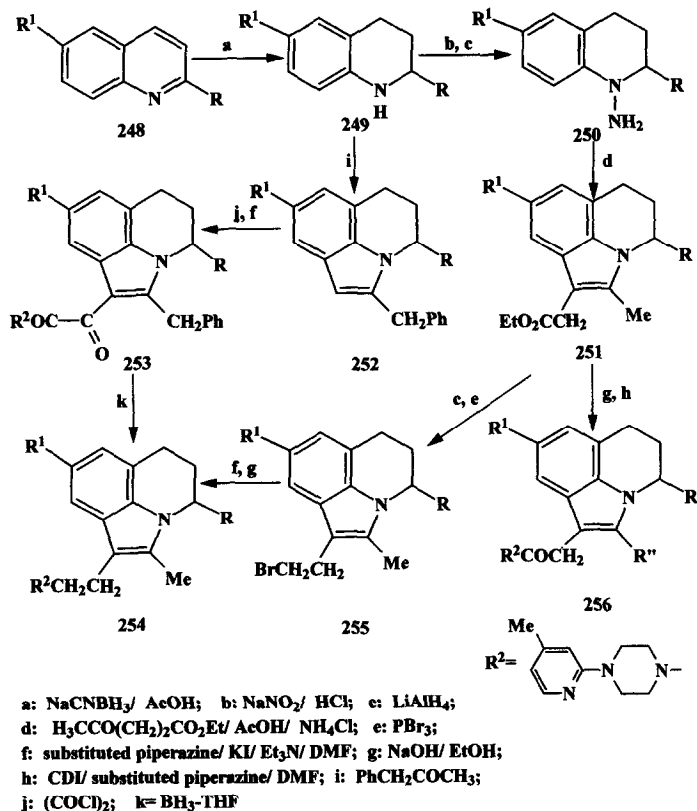


Scheme 44

Irradiation of lomefloxacin **271** in dilute neutral aqueous solution (in which it exists as a zwitter ion) in Pyrex-filtered 500 W medium pressure mercury (Helios Italquartz) at  $17^\circ\text{C}$  gave pyrrolo[3,2,1-*ij*]quinoline **272** (99JOC5388). Under this condition, reductive defluorination via a radical anion took place. This study is important because of the phototoxicity of the fluorinated compounds which could be used as antibacterials (Scheme 49).

Regiospecific intramolecular cyclization of 3-carbomethoxyindole-1-propionic acid **273** with PPA took place on the 7-position to afford pyrroloquinoline **274** with no cyclization at the 2-position (86H2109) (Scheme 50).

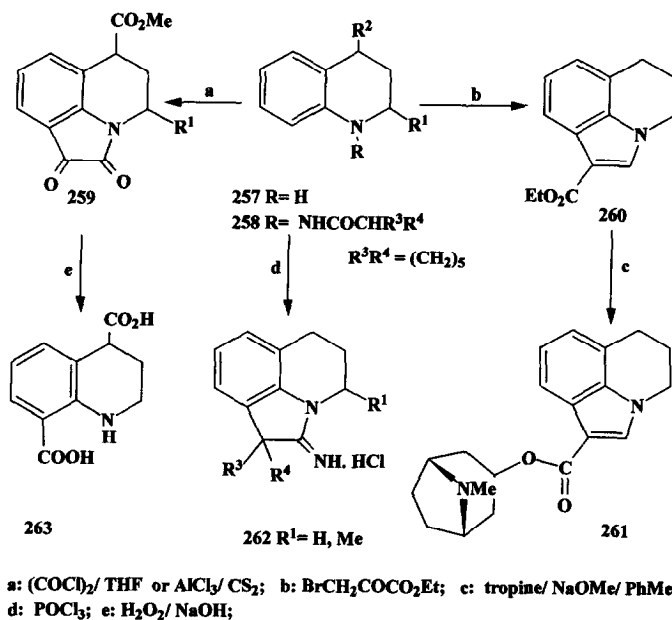
Bromination of the aniline derivative **275** with  $\text{Br}_2$  in presence of  $\text{K}_2\text{CO}_3$  afforded the 2-bromo derivative **276** which upon treatment with  $\text{Bu}'\text{OCl}$  followed by ethylthioacetone gave the indole derivative **277**. Removal of the bromine and the ethylthio group by treatment with Rany Nickel followed by reduction with  $\text{Sn}/\text{HCl}$  gave the indoline **278**. Subsequent reaction with ethoxymethylenemalononic ester (EMME) gave the enamine ester that upon cyclization with PPA and hydrolysis with  $\text{HCl}$  gave the pyrroloquinoline-3-carboxylic acid **279**. Displacement of the fluorine with cyclic amines gave 9-heterocyclicamino derivative **280** as antibacterials (90EP390135). Nitration of **279** gave the corresponding 7-nitro derivative **281** whose reduction afforded the amino derivative **282** that upon reaction with cyclic amines



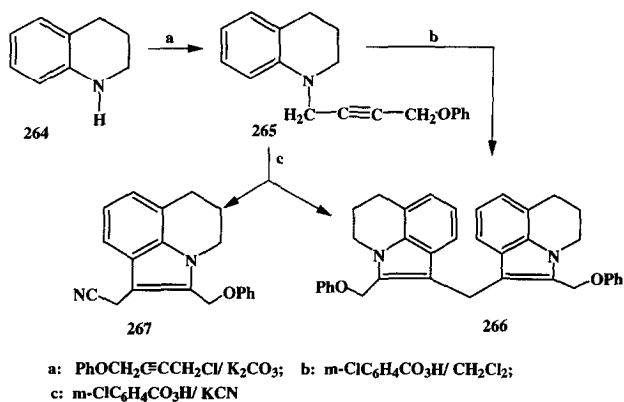
### Scheme 45

gave the 9-cyclic amino derivatives **283** (90CPB2459). The latter compounds were tested for antibacterial activity against gram-positive *S. aureus* and *Streptococcus pyogenes* IID S-23 and gram-negative *E. coli* and *Pseudomonas aeruginosa* (90CPB2459). Some cephaloglycine derivatives of pyrroloquinolines were prepared (87SUP1336949) (Scheme 51).

Reaction of trifluoronitrobenzene **284** with ethyl acetoacetate in presence of NaH followed by hydrolysis and decarboxylation afforded the acetonyl derivative **285** which upon reduction with borohydride gave the isopropanol derivative **286**. Catalytic reduction of **286** gave the corresponding amine which upon condensation with ethoxymethylene malonate gave **287** (88JHC1567). Cyclization using Mitsunobu procedure gave the indole derivative **288**. Cyclization of **288** with PPA afforded the pyrroloquinoline carboxylic acid ester which was hydrolyzed to the free acid **289** (88JHC1567) (Scheme 52).

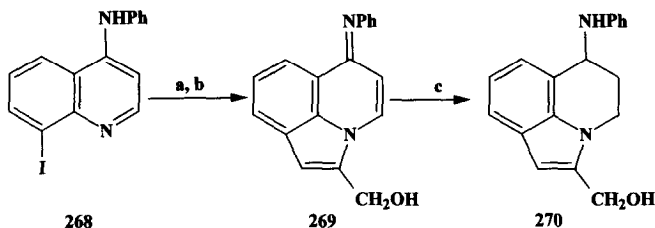


Scheme 46



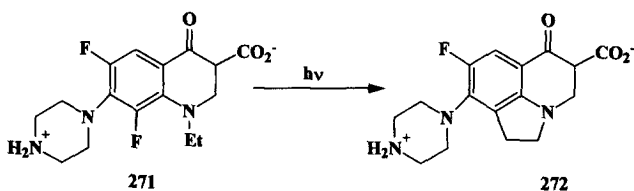
Scheme 47

Treatment of the indole derivative **290** with trifluoroacetic acid gave the addition product **291** that upon cyclization afforded the pyridoindole derivative **292** (81H713). Treatment of **290** which has a dioxopiperazine ring on C-3 with boron trifluoride etherate gave a mixture of pyrroloindole **293**

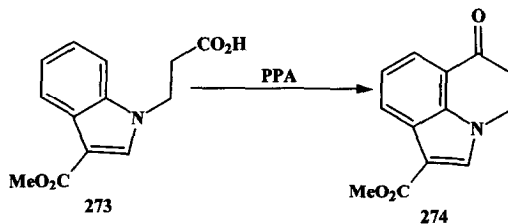


a:  $\text{HC}\equiv\text{CCH}_2\text{OH}/\text{Et}_3\text{N}$ ; b:  $\text{PhI}(\text{Ph}_3\text{P})_2\text{Pd}/\text{CuI}$ ; c:  $\text{H}_2/\text{Lindlar's catalyst}$

Scheme 48



Scheme 49

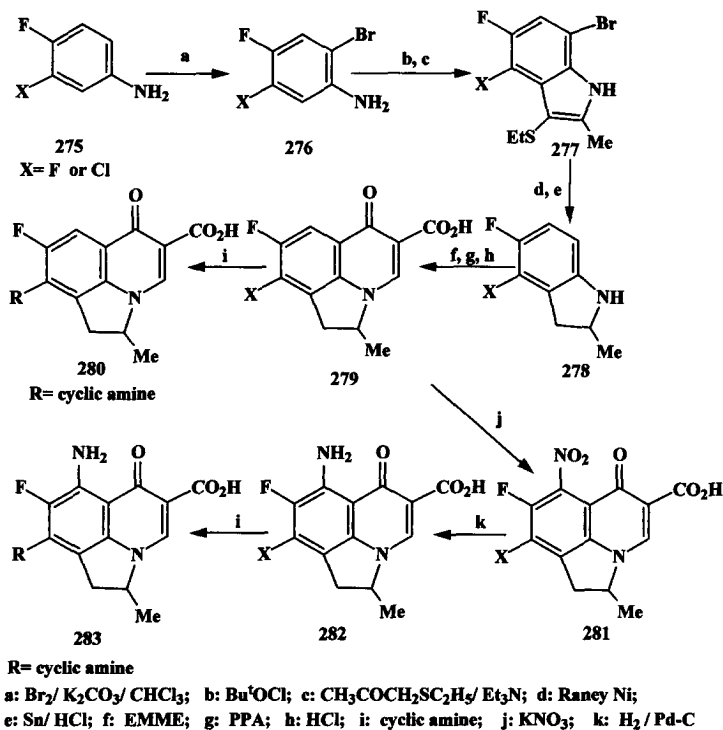


Scheme 50

and pyrroloquinoline **294** (79JCS(P1)3053). Their ratios depend on the reaction condition whereby the stronger Lewis acid, boron tribromide led to **294** as the major product, with other products, but no trace of **293** was detected. Cyclization of **294** to **295** did not take place in TFA since the later is unstable and opened to **294** (Scheme 53).

Heating the indole derivatives **296** with **297** gave **298** that were cyclized to give **299** (82JAPK8202285). On the other hand, reaction of **296** with ethoxymethylenemalonate gave **301** that upon cyclization with PPA gave **300** which upon hydrolysis with NaOH gave the corresponding acid **299** (83JAPK5813585, 78JAPK7882799). Compounds of the type **299** possess bactericidal activity stronger than nalidixic acid (78JAPK7882799) (Scheme 54).

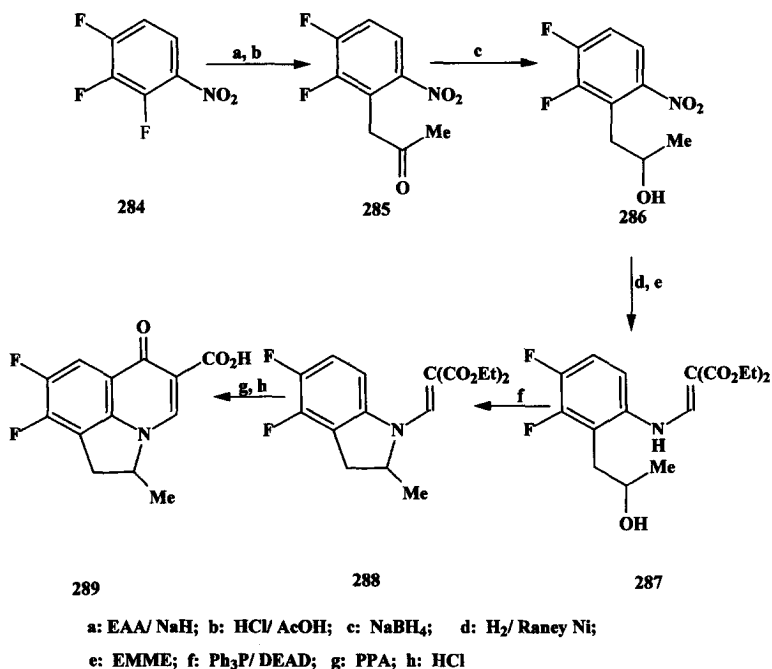
A series of optically active substituted 1,2-dihydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acids were prepared (95CPB1678).



Scheme 51

Thus, starting with the optically active alcohol **302**, compound **303** was prepared via mesylation and cyclization that upon constructing the pyridine ring gave difluoropyrroloquinoline-5-carboxylic acid **305** via **304**. Nitration of **305** gave the 7-nitro derivative **306** that upon catalytic hydrogenation afforded the corresponding amine **307**. Their condensation with cyclic amines (pyrrolidine, piperazine and morpholine derivatives) in hexamethylphosphotriamide (HMPA) and in presence of pyridine gave the corresponding 9-cyclic amino derivatives **308** whose antibacterial activities were studied. Similarly, reaction of **305** with amines gave **309** (95CPB1678). Various heterocyclic amines at C-3 and their biological activities were reported (84EP115334, 84JAPK5978189, 87JAPK6233188, 92JAPK04139126) (Scheme 55).

Formylation of the *N*-allyl indole derivatives **311** (obtained by allylation of the indole **310**) afforded 1-allyl-7-formyl-indole **312**. Subsequent condensation of 7-formyl indole derivatives **312** with ethyl acetate in presence of sodium ethoxide gave **313** (89S322). Reaction of **312** with *N*-methylhydroxylamine hydrochloride afforded the cycloadduct, tetracyclic



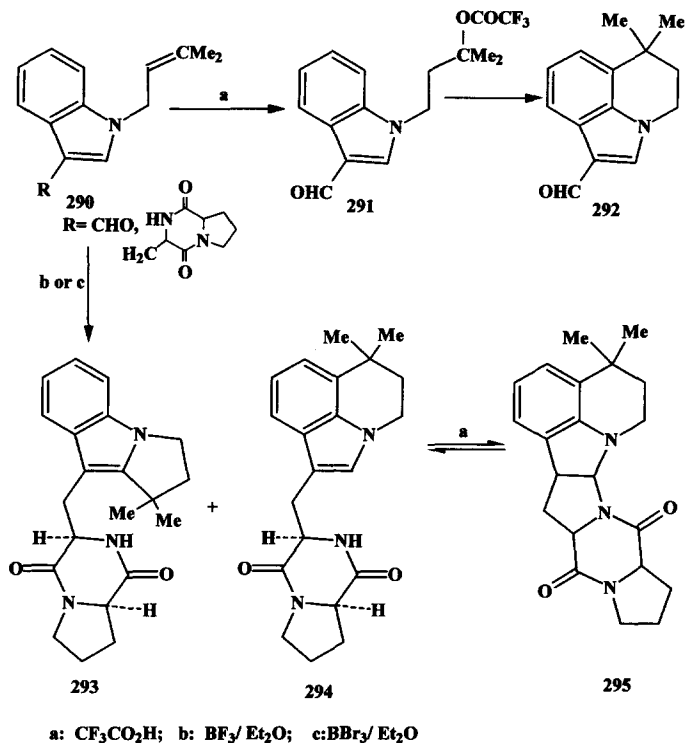
Scheme 52

isoxazopyrroloquinoline **314**. Their formation was explained to be due to intramolecular 1,3-dipolar cycloaddition of the nitrones presumably formed from **312** (93AJC843). Reduction of **314** with LiAlH<sub>4</sub> gave the tricyclic pyrroloquinoline derivative **315** (Scheme 56).

Bromination of the diphenyl indole derivative **316** with bromine in DMF or trimethylammonium bromide afforded the 7-bromo derivative **317**. Reaction with allyl bromide or its derivatives gave *N*-allyl derivatives **318** that upon cyclization with palladium acetate gave 7,9-dimethoxy-1,2-diphenylpyrrolo[3,2,1-*ij*]quinoline derivatives **319** (92T7601) (Scheme 57).

Cyclization of *N*-acryloylindolines **320** using typical Heck condition by heating with Pd(AcO)<sub>2</sub> gave **321** and **322** (1%). Cyclization of the trisubstituted *N*-acryloylindolines **320** under the same conditions gave **324** (85%) together with **323**. It was found that increasing the substitution on the acryl group decreases the yield of the cyclization products (95JOC2312). Similarly, **325** was obtained (96HC555) (Scheme 58).

Cyanoethylation of 2-phenylindole (79M1585) and dimethylindole (82AP901) gave the corresponding cyanoethyl derivatives **326** whose hydrolysis to the acids **327** and subsequent cyclization with PPA gave **328**.



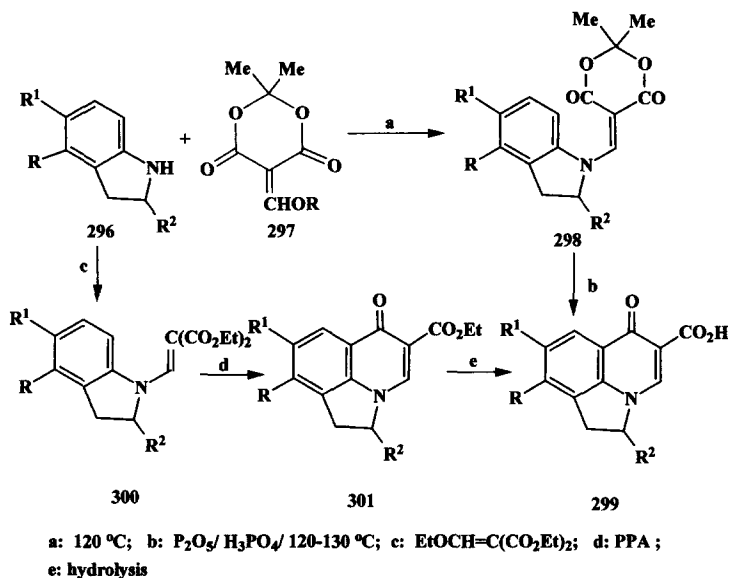
Scheme 53

Dehydrogenation of the later with Pd/C gave **329** (82AP901). On the other hand, reaction of indoline or 2-methylindoline with acrylic acid or crotonic acid by heating in presence of polyphosphoric acid gave **330** and **331** (79JHC949) (Scheme 59).

The aniline derivative **332**, prepared from 2-fluoro-6-nitrotoluene, was transformed through successive reactions as shown in Scheme 60 to give the functionalized indole **333**. It was then reduced with  $\text{LiAlH}_4$  to the dimethylaminopropyl derivative which was quaternized with MeI to the trimethyl ammonium salt **334**. Subsequent cyclization and functionalization afforded the pyrroloquinoline **335**. The latter could be transformed to the tetracyclic acid **336** (90JHC2151). (Scheme 60)

Reaction of *o*-toluidine with chloral hydrate in presence of hydroxylamine hydrochloride and subsequent treatment with  $\text{H}_2\text{SO}_4$  gave the isatin derivative **337**. Bromination of **337** followed by reaction with sodium diethyl malonate gave **338**. Catalytic reduction with Pd/C gave the oxoindole derivative **339** that upon hydrolysis with aqueous NaOH followed by

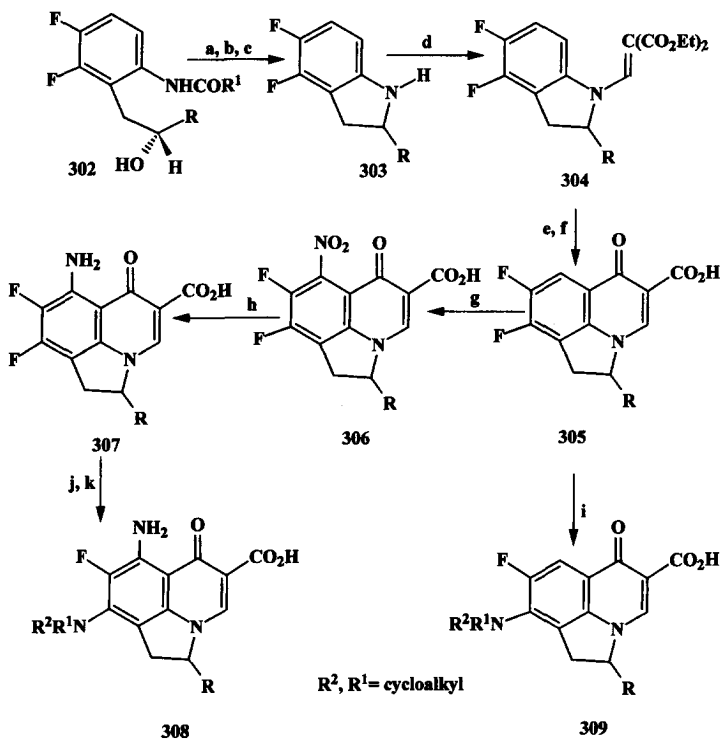




Scheme 54

acidification by acidic ion exchange resin gave the acid **340**. Intramolecular cyclization of **340** with  $\text{Ac}_2\text{O}$  afforded **341** (90JOC560) (Scheme 61).

The products from the reaction of diethyl malonate with dihydroindole **342** was found to be dependent upon the reaction conditions. Thus, reaction with 0.5 mol of malonic ester afforded **343** which could be cyclized to the pyrroloquinoline **344** by the action of a mixture of aluminium chloride and sodium chloride. The use of 1 mol of the substituted malonic esters gave the respective pyrroloquinolines **344** and **345**. The benzyl group could be readily removed by treatment with  $\text{AlCl}_3/\text{NaCl}$ . On the other hand, reaction with 2 mol of the diethyl malonate afforded the pyranopyrroloquinoline **355** which upon heating with  $\text{NaOH}$  and then  $\text{HCl}$  gave **356** that was deacetylated upon treatment with conc.  $\text{H}_2\text{SO}_4$ . Treatment of **355** with  $\text{SOCl}_2$  in dioxane gave the dichloroacetyl derivative **347** which upon reaction with  $\text{NaN}_3$  afforded the tetrazole derivative **358**. Nitration of **355** gave the nitro derivative **356**. Coupling with diazoaniline gave **357** (89JHC1555). Several reactions had been carried out on the pyrroloquinoline derivatives **344**. Thus, nitration of **344** ( $\text{R}=\text{H}$ ) gave the 5-nitro derivative **348** which upon chlorination afforded the 5-chloro-5-nitroderivative **349**, whose azidolysis gave the 5,5-diazido product **350**. Alternatively, chlorination of **344** with  $\text{SO}_2\text{Cl}_2$  afforded the 5,5-dichloro derivative **351** which upon reaction with  $\text{NaN}_3$  gave **350**. On the other hand,



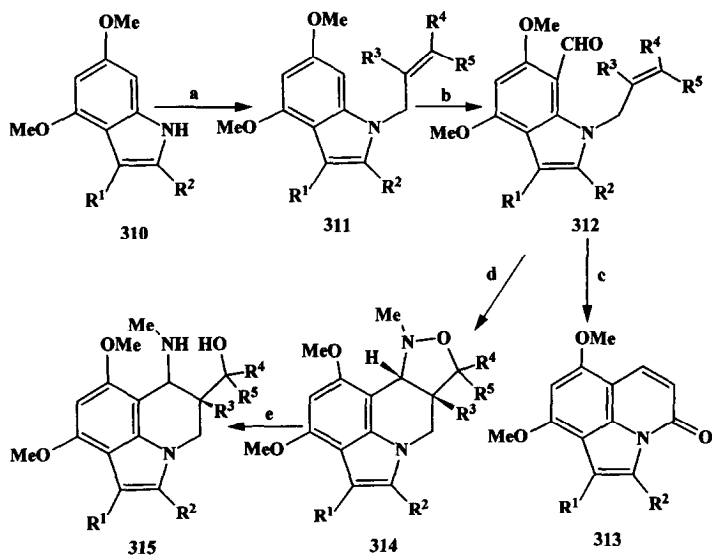
a:  $\text{MeSCl}/\text{Et}_3\text{N}$ ; b:  $\text{K}_2\text{CO}_3$ ; c:  $\text{KOH}$ ; d:  $\text{EMME}$ ; e:  $\text{PPA}$ ; f:  $\text{HCl}/\text{AcOH}$ ;  
 g:  $\text{KNO}_3$ ; h:  $\text{H}_2/\text{Pd-C}$ ; i:  $\text{R}^2\text{R}^1\text{NH}/\text{HMPA}$ ; j:  $\text{BF}_3/\text{Et}_2\text{O}/\text{HMPA}$ ;  
 k:  $\text{R}^2\text{R}^1\text{NH}/\text{Et}_3\text{N}$ ;

Scheme 55

chlorination of **344** with  $\text{POCl}_3$  gave the corresponding 6-chloro derivatives **352** whose treatment with  $\text{NaN}_3$  gave the 6-azido derivative **353** that upon catalytic reduction using  $\text{Pd/C}$  gave the corresponding amino derivative **354**. Treatment of **352** ( $\text{R} = \text{Ph}$ ) with  $\text{NaN}_3$  afforded the indolopyrroloquinoline **359** (89JHC1555) (Scheme 62).

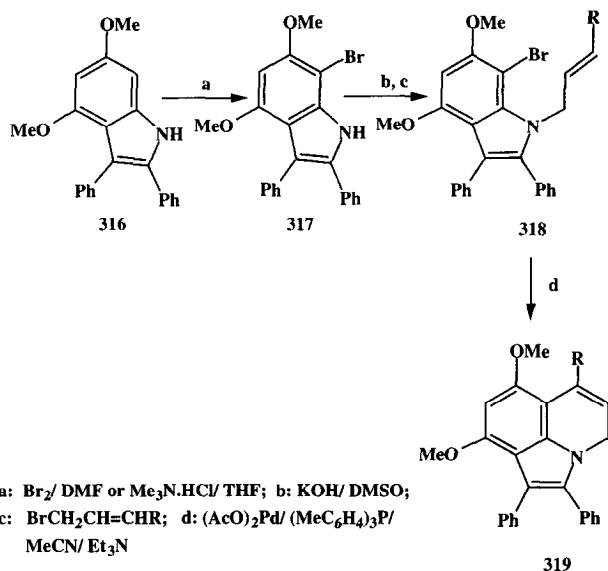
The reaction of methane tricarboxylate with indoline **342** gave the tricyclic derivative **361** which can be transformed to the amide derivatives **362** (97JHC969). Alkylation of the *N*-benzyl indoline **360** with pentafluoroacetone gave **363** which upon debenzilation and subsequent acylation with diketene followed by cyclization gave **364**. Other haloacetones were used to prepare different halogenated derivatives (79BEP872311) (Scheme 63).

Regioselective lithiation of the formamidine **365** followed by tosylation afforded the corresponding 7-sulfone **367** which upon reaction with



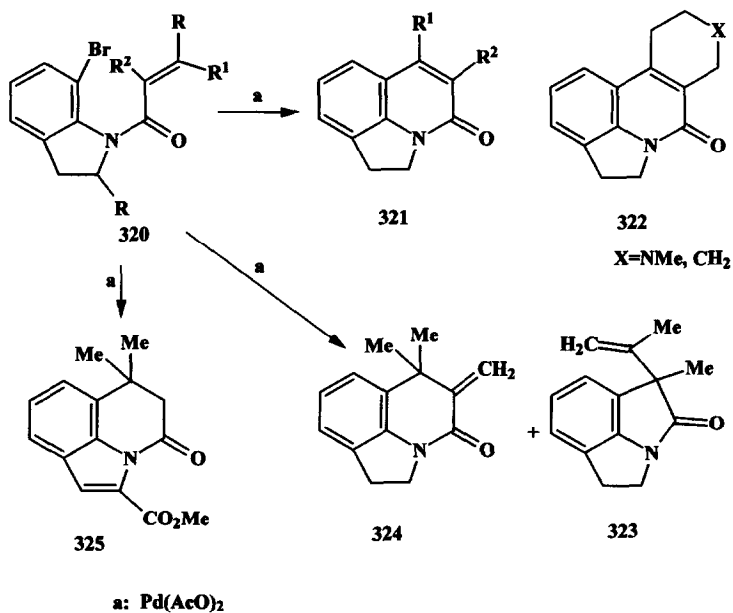
a:  $R^4R^5C=CR^3CH_2Br$  / DMSO; b: DMF/  $POCl_3$ ; c:  $EtOAc/NaOEt$ ;  
d:  $MeNH.OH.HCl/AcONa/EtOH$ ; e:  $LiAlH_4$

Scheme 56

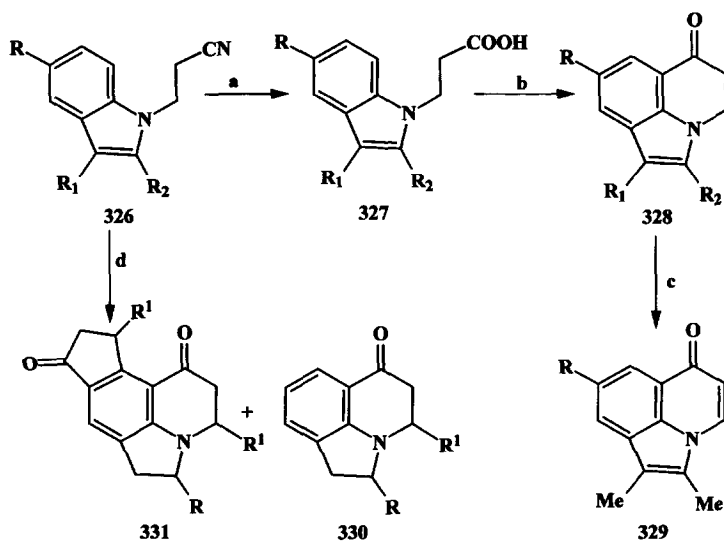


a:  $Br_2$ / DMF or  $Me_3N.HCl/THF$ ; b:  $KOH$ / DMSO;  
c:  $BrCH_2CH=CHR$ ; d:  $(AcO)_2Pd/(MeC_6H_4)_3P/MeCN/Et_3N$

Scheme 57

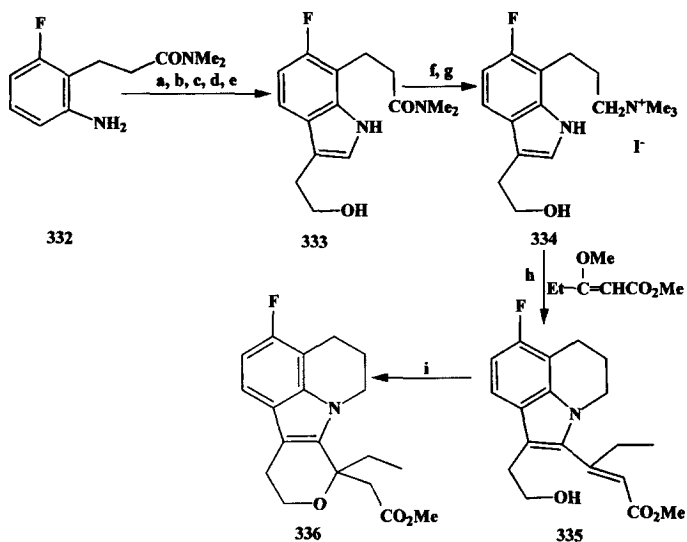


Scheme 58



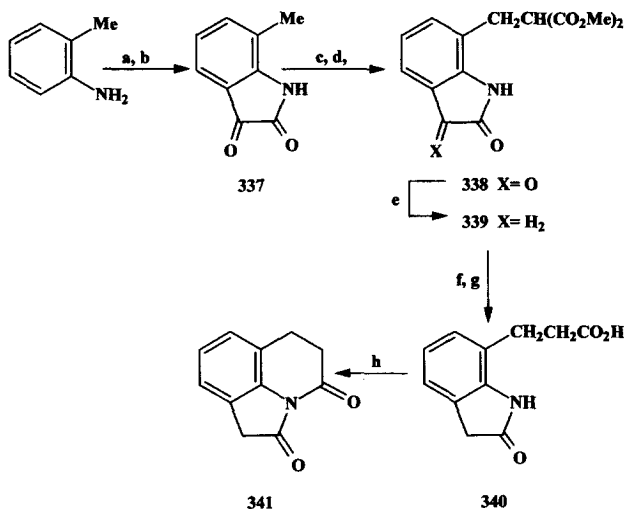
$a$ : hydrolysis;  $b$ : PPA;  $c$ : Pd-C;  $d$ : R<sup>1</sup>CH=CHCO<sub>2</sub>H/PPA

Scheme 59



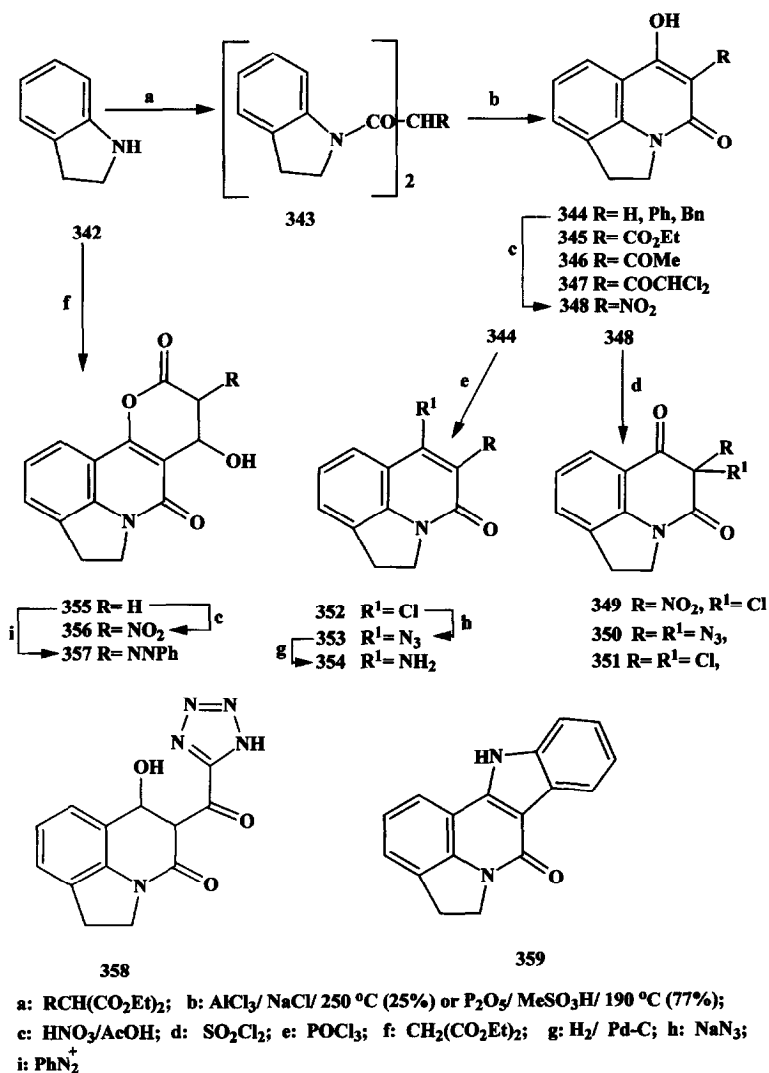
a:  $\text{NaNO}_2/\text{HCl}/\text{H}_2\text{O}$ ; b:  $\text{SnCl}_2$ ; c:  $\text{H}_2/\text{Pd-C}$ ; d: dihydrofuran/THF/ $\text{H}_2\text{O}$ ; e:  $\text{ZnCl}_2$ /ethylene glycol/heat; f:  $\text{LiAlH}_4$ ; g:  $\text{MeI}/\text{THF}$ ; h: Amberlite IRA-400(OH)/heat; i:  $\text{BF}_3/\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$

Scheme 60



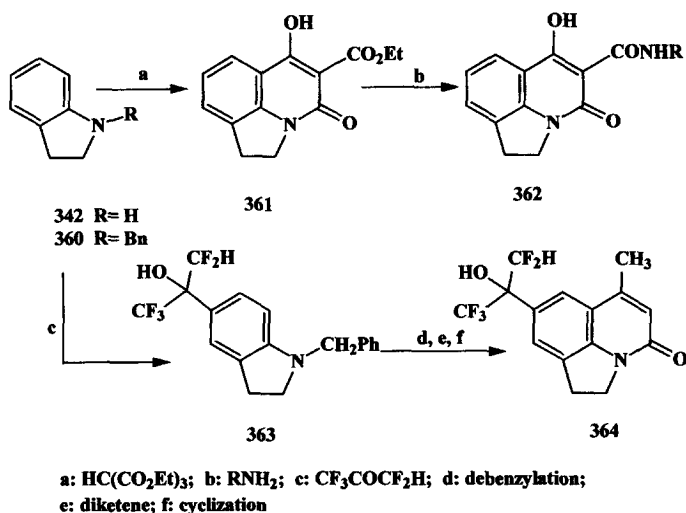
a:  $\text{Cl}_3\text{CCH}(\text{OH})_2/\text{NH}_2\text{OH}/\text{H}^+$ ; b:  $\text{H}_2\text{SO}_4$ ; c:  $\text{Br}_2/h\nu$ ; d:  $\text{NaCH}(\text{CO}_2\text{Me})_2$ ; e:  $\text{H}_2/\text{Pd-C}$ ; f:  $\text{HO}^*/\text{H}_2\text{O}$ ; g:  $\text{H}^*/\text{H}_2\text{O}$ ; h:  $\text{Ac}_2\text{O}$

Scheme 61



Scheme 62

bromopropionyl chloride gave **368** that cyclized upon treatment with Bu<sub>3</sub>SnH (TBTH) and AIBN to the pyrroloquinoline **369** (96JCS(P1)675). On the other hand, treatment of **367** with a mixture of AlCl<sub>3</sub>/KCl/NaCl gave a mixture of **369** (85%) and **370** (5.5%) (84JAPK59134792). Friedel Craft cyclization of chloropropionylindole derivative **366** afforded the

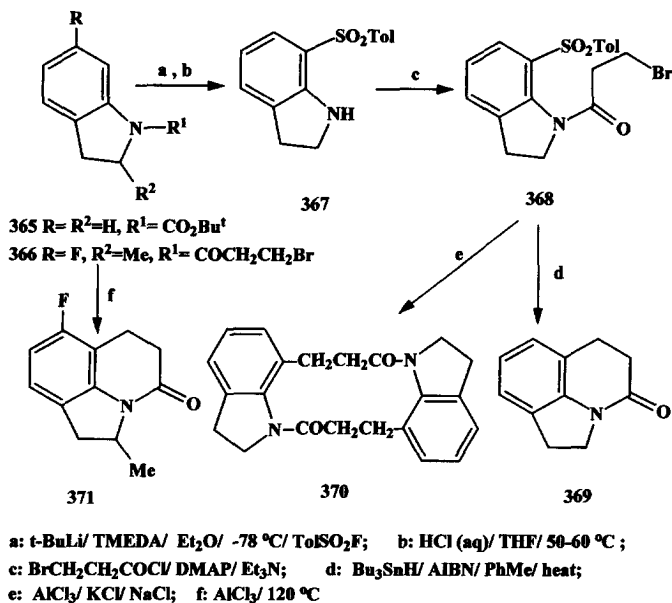


Scheme 63

corresponding pyrroloquinoline **371** which gave 100% control of *Pyricularia oryzae* on rice seedlings (97EP807631) (Scheme 64).

Reaction of pyrroloquinoline **372** with the aldehyde **373** afforded **374** that could be reduced to **375** which is useful as a serotonin antagonist (90EP375045). The azodye **376**, which was prepared from the coupling of the respective pyrroloquinoline with diazotized 2-amino-3-(methoxycarbonyl)-5-isobutyrylthiophene, was used for dyeing polyamide fabrics in a fast reddish-blue shade (89GEP3840097). Reaction of pyrroloquinoline 2-carboxylate ester with ethylene diamine in presence of trimethyl aluminium gave the imidazolidine derivative **377** which is useful as antihypotensive and antidepressant (85EP139584) (Scheme 65).

Hydrolysis of the pyrroloquinoline **378** afforded the corresponding acid **379** which upon treatment with 1,1'-carbonyldiimidazole followed by piperazine derivatives afforded 5,6-dihydro-2-methyl-1-[2-substitutedpiperazinyl]-4*H*-pyrrolo[3,2,1-*ij*]quinoline **381**. Reduction of **381** afforded the corresponding piperazinylethyl derivative **386**. Alternatively, the later could be obtained by reduction of **378** to afford the 1-ethanol derivative **384** that upon bromination with  $\text{PBr}_3$  gave the bromoalkyl **385**, which upon condensation with piperazine derivative gave **386**. Nitration of **379** gave the 8-nitro derivative **380** that upon reaction with CDI and piperazine analogs gave **382**. Hydrogenation of **382** and then benzoylation gave the corresponding benzamido derivative **383** (95JMC669) (Scheme 66).



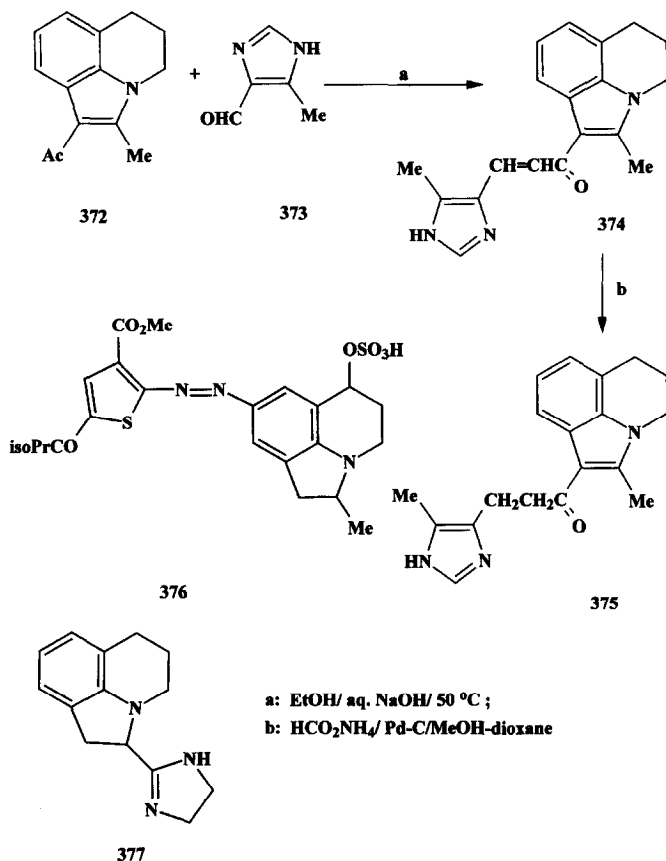
Scheme 64

Dehydrogenation of **387** with  $Ph_3CBF_4$  gave **388** which upon reaction with  $P_4S_{10}$  gave the corresponding thione **389** that methylated with  $MeI$  to give **390**. Reaction of **390** with aniline or its derivatives gave **394**. Condensation of either **388**, **389** or **390** with tetrachlorocyclopentadiene afforded **391** (79AP801). Reaction of the azapseudophenalenone **388** with malononitrile gave **392** and with  $R_3OBF_4$  gave the salt **393** (82M623) (Scheme 67).

### 3. Pyrrolo[2,1-j]quinolines

This ring system exists in various marine alkaloids such as lepadiformine (94TL2691, 99JOC686), cylindricines (93T8645, 95AJC955) and fascicularin (97TL363) which were isolated from the ascidians *Clavelina lepadiformis*, *Clavelina cylindrica* and *Nephteis fascicularis*. Stereoisomers of lepadiformine and 11-deoxycylindricine C were prepared. Thus, condensation of **395** with the cyclohexanone derivative **396** followed by cycloaddition with  $CH_2=CHSPh$  afforded the pyrrolidine **397** as a single stereo and regio isomer. Hydrolysis of **397** with acid followed by reduction and cyclization gave **398**. Ozonolysis and then reduction gave **399** (97TL3369). A



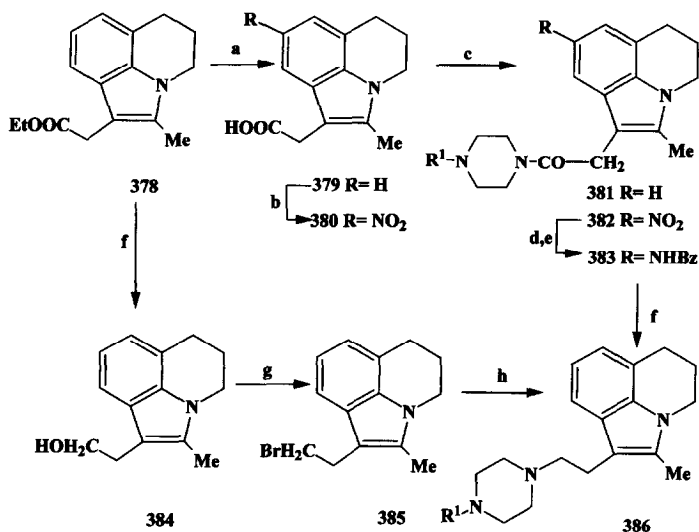


Scheme 65

stereoselective synthesis of lepadiformine via an intramolecular nitron 1,3-diene dipolar cycloaddition was recently reported (99JOC686) (Scheme 68).

Synthesis of the diastereoisomers **407** and **408** of lepadiformine had been achieved. Thus, **400** was converted to **402** via **401**. Desulfoxidation of **402** with Na<sub>2</sub>CO<sub>3</sub> afforded dihydropyrrole, that epimerized to give the isomers **403**. Catalytic hydrogenation gave the pyrrolidine derivative **404**. Further reduction of **404** with LiEt<sub>3</sub>H followed by benzylation afforded the *O*-benzyl derivatives **405** and **406**. Cyclization upon treatment with MeLi and subsequent reduction with NaBH<sub>4</sub> and then debenzoylation afforded **407** and **408** (99JOC688) (Scheme 69).

A total synthesis for (+)-cylindricines A and B has been achieved. Alkylation of β-trifluoromethanesulfonyl ester **409** afforded **410** (93MI273)

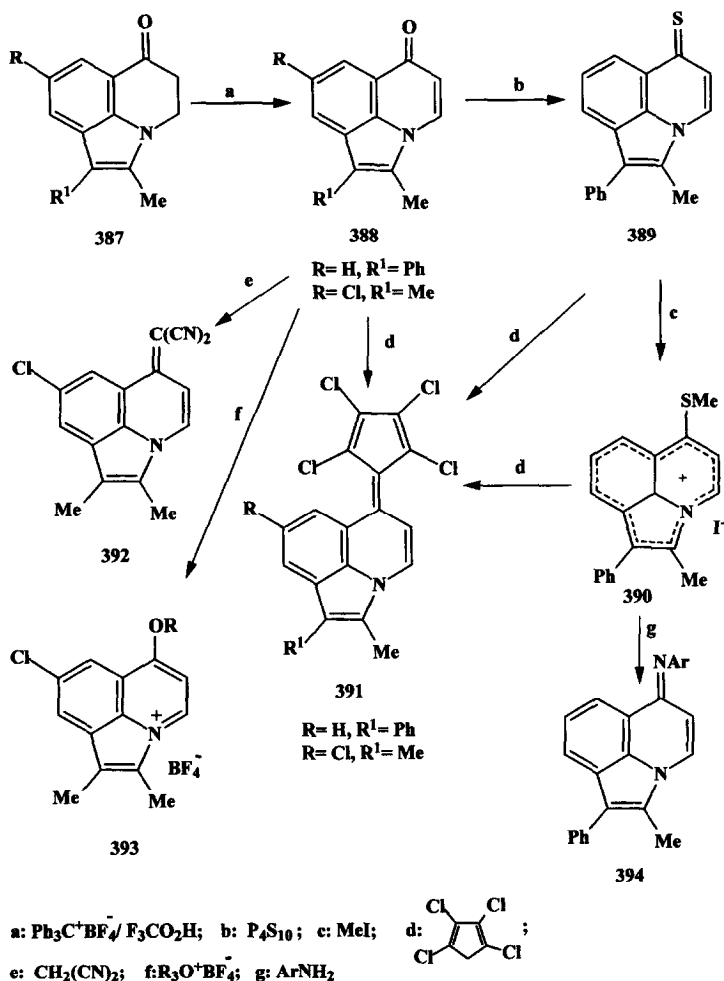


a: NaOH/EtOH; b: HNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub>; c: CDI/substituted piperazine/DMF; d: H<sub>2</sub>/Pd-C; e: BzCl; f: LiAlH<sub>4</sub>/THF; g: PBr<sub>3</sub>/CHCl<sub>3</sub>; h: substituted piperazine/ KI/ Et<sub>3</sub>N/ DMF

Scheme 66

which upon treatment with lithium anion of dimethyl methylphosphonate gave the  $\beta$ -ketophosphonate **411** (99JOC8263) that upon reaction with C<sub>6</sub>H<sub>13</sub>CHO afforded the dienone **412**. Double Michael addition of ammonia gave **413** which upon treatment with *N*-chlorosuccinimide followed by cyclization afforded the tricyclic product **414** (99JOC8263), which upon separation gave cylindricine A that can be converted to the natural mixture of cylindricines A and B through standing in C<sub>6</sub>D<sub>6</sub> (93T8645) as shown in Scheme 70.

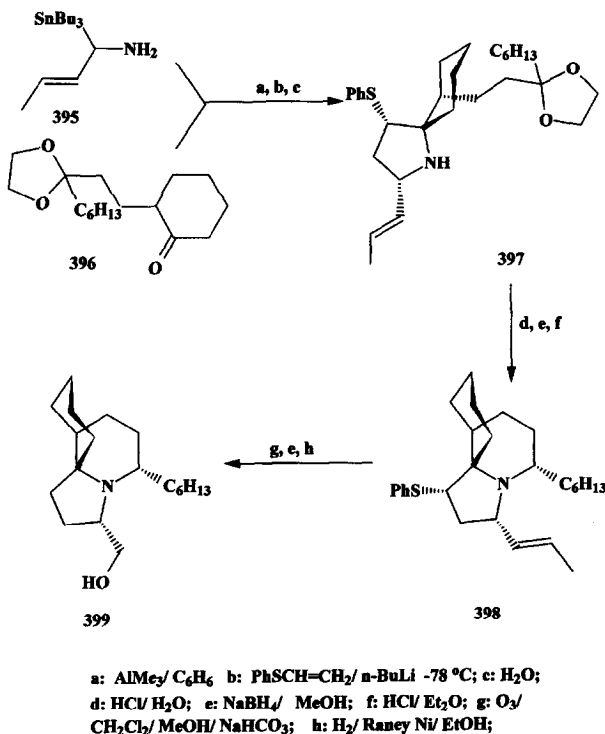
Synthesis of (+)-cylindricines A, D and E are outlined in Scheme 70. Reaction of the cyclohexanone **415** with butenyl magnesium bromide followed by heating with dilute HCl gave **416** which upon treatment with octyne lithium afforded the propargyl alcohol **417** that was selectively reduced with LiAlH<sub>4</sub> to afford **418**. Oxidation of **418** with MnO<sub>2</sub> gave the dienone **419** which was cyclized upon heating with ammonia and ammonium chloride to give a mixture of the stereoisomers **420**, **423** and **424**. Treatment of **420** with *N*-chlorosuccinimide gave the corresponding chloro derivative which upon radical cyclization using CuCl/CuCl<sub>2</sub> in tetrahydrofuran and acetic acid afforded a mixture of cylindricine A (R = Cl) **422** and *epi*-cylindricine A (R = Cl) **423** which were separated by



Scheme 67

flash chromatography. Blackman cyclization of the chloro derivative followed by treating the crude mixture with sodium methoxide in methanol gave a mixture of cylindricine D ( $\text{R}=\text{OMe}$ ) and epi-cylindricine D ( $\text{R}=\text{OMe}$ ) (97JOC5630) (Scheme 71).

Cycloaddition of 4-acylsubstituted fulvene **425** with the imine **427** in boiling toluene gave the tricyclic pyrroline **428**. Treatment of **426** with **427** and subsequent reaction of the product **429** with malononitrile gave **428** (86S908) (Scheme 72).



Scheme 68

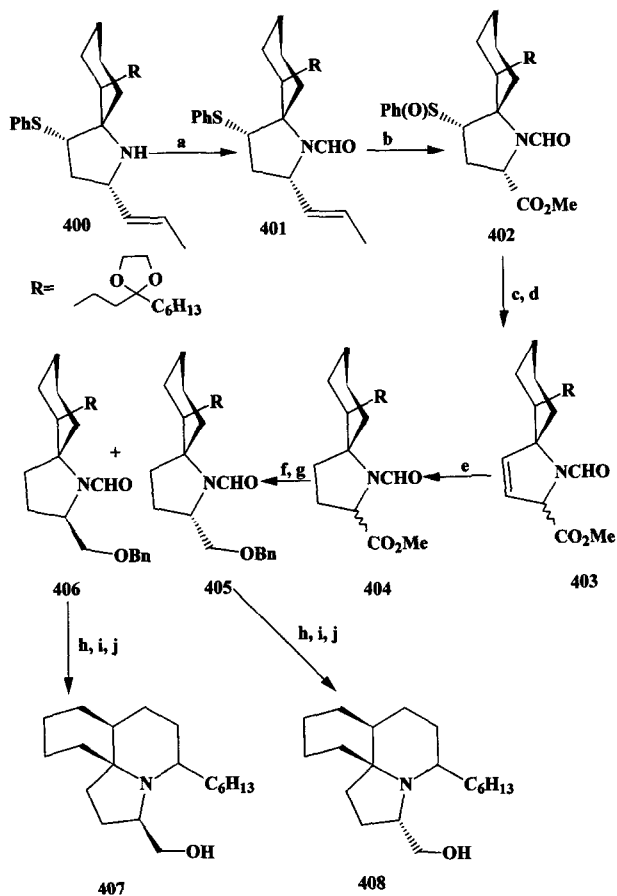
## V. Five Membered Heterocyclo-Quinolines with Two Heteroatoms

### A. PYRAZOQUINOLINES

Three classes of ring systems of the pyrazoquinoline type are possible (Fig. 5). However, compounds of only pyrazo[1,5-*a*]quinoline and pyrazo[4,5,1-*ij*]quinoline are known. On the other hand, no examples of the pyrazo[5,1-*j*]quinoline, to the best of our knowledge, are reported.

#### 1. Pyrazo[1,5-*a*]quinolines

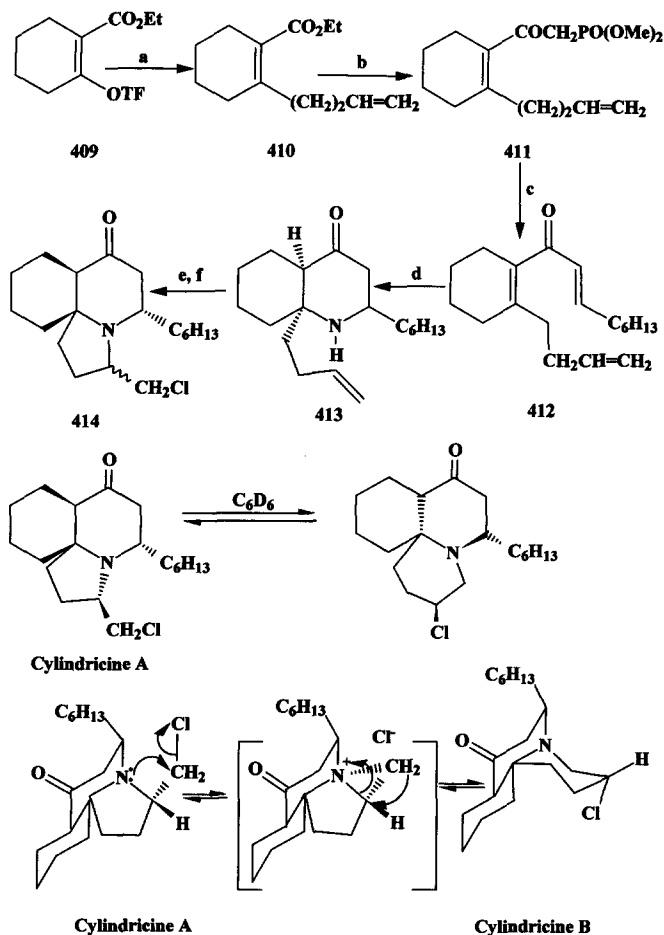
Pyrazo[1,5-*a*]quinolines were synthesized by reaction of acrylates with 1-(*N*-methylamino)quinolines **430** to afford the corresponding Michael addition product **431** which upon dehydrogenation with DDQ gave **432**.



**a:**  $\text{MeCO}_2\text{CHO}/\text{NEt}_3$ ; **b:**  $\text{O}_3, \text{NaOH}/\text{MeOH}/\text{CH}_2\text{Cl}_2/-78^\circ\text{C}$ ;  
**c:**  $\text{Na}_2\text{CO}_3/\text{PhMe}$ ; **d:**  $\text{DBU}/\text{THF}$ ; **e:**  $\text{H}_2/\text{Pd-C}/\text{MeOH}$ ;  
**f:**  $\text{LiBEt}_3\text{H}/\text{THF}$ ; **g:**  $\text{NaH}/\text{THF}/\text{BnBr}$ ; **h:**  $\text{MeLi}/\text{THF}$ ;  
**i:**  $\text{NaBH}_4/\text{MeOH}$ ; **j:**  $\text{H}_2/\text{Ra-Ni}/\text{EtOH}$

Scheme 69

Selective hydrolysis of the 3-carboxylate with 6 N-HCl/AcOH was unsuccessful and instead the 4-carboxylate hydrolyzed to the corresponding acid, however, heating of **432** at  $50^\circ\text{C}$  caused its hydrolysis and decarboxylation in one step. Subsequent reaction with either  $\text{MnO}_2$  or DDQ gave **433**. The fluorine atom at 8-position could be replaced by cyclic amines to give the 8-pyrrolyl or 8-[1-methyl-4-piperazinyl] derivatives **436** which upon hydrolysis using either acidic or basic conditions afforded the

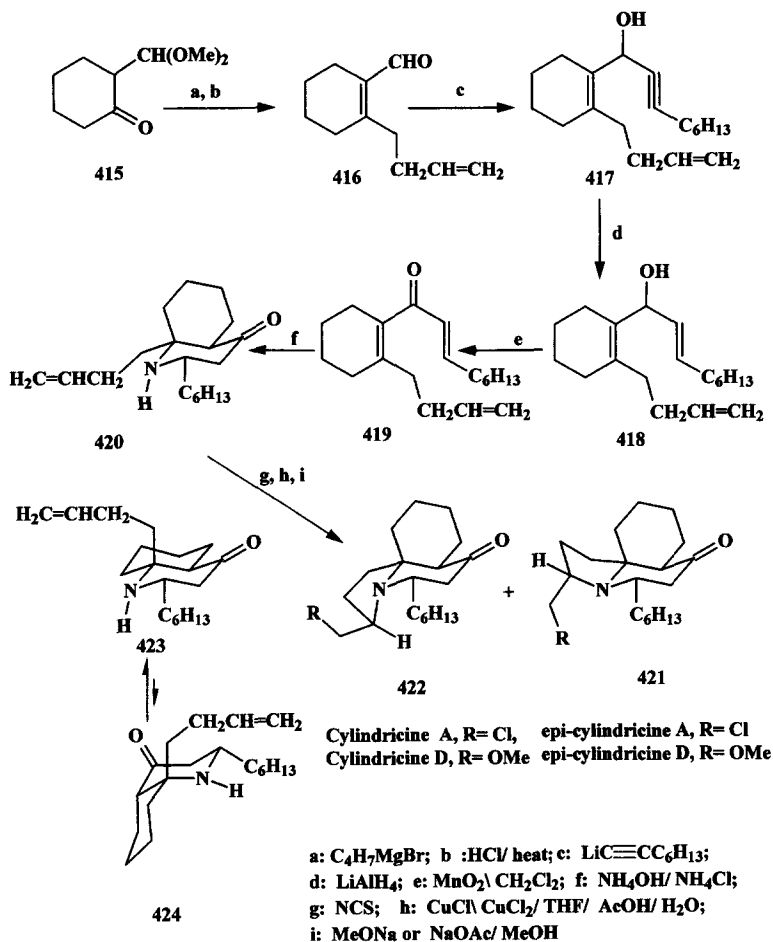


a:  $\text{CH}_2\text{CHCH}_2\text{CH}_2\text{Cu}(\text{CN})\text{Li}/\text{Et}_2\text{O}/-50^\circ\text{C}$  99%; b:  $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2/\text{THF}/-78^\circ\text{C}$ ; c:  $\text{C}_6\text{H}_{13}\text{CHO}/\text{LiCl}/i\text{-Pr}_2\text{NEt}/\text{CH}_3\text{CN}$ ; d:  $\text{NH}_3/\text{EtOH}/\text{conc. NH}_4\text{OH}$ ; e:  $\text{NCS}/\text{CH}_2\text{Cl}_2$ ; f:  $\text{CuCl}/\text{CuCl}_2/\text{THF}/\text{H}_2\text{O}/\text{AcOH}$

Scheme 70

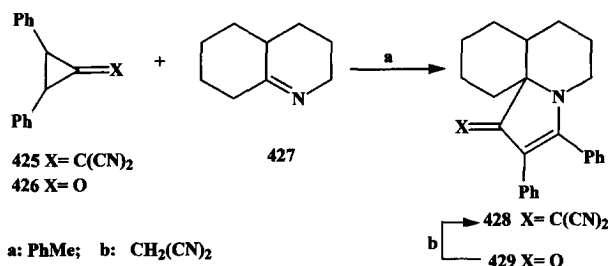
corresponding acid **437**. Reaction of **430** with 2-chloroacetonitrile and subsequent treatment with DDQ in benzene afforded **435** which upon treatment with  $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$  followed by N-demethylation with 6 N-HCl/AcOH and then methylated with  $\text{MeI}/\text{K}_2\text{CO}_3$  in DMF gave **434**. Some of the acid derivatives **437** were DNA gyrase inhibitors (96T8471) (Scheme 73).

Reaction of **438** with acetylacetone gave **439** (92MI151). Bromination of **439** gave the corresponding 3,4-dibromo derivative **441**, where the acyl



Scheme 71

group at position 3 was split off. On the other hand, treatment of **441** with *p*-nitrophenylhydrazine gave **442** whose bromination generates **441**. Treatment of **439** with sulfuric acid caused elimination of the acetyl group to give **443**. Bromination of the 5-methoxy derivative of **445** obtained by methylation of **439** gave the 3-bromo derivative **444** (95ZOR447, 93MI99). Displacement of the 8-halogen atom of **439** with *N*-methyl piperazine gave **440** (95ZOR447). The role of the functional groups in compounds of the type **439** was aided by studying the tautomeric equilibrium, by NMR spectroscopy, and used to wide the range of chemical modifications in these compounds (95ZOR447) (Scheme 74).



Scheme 72

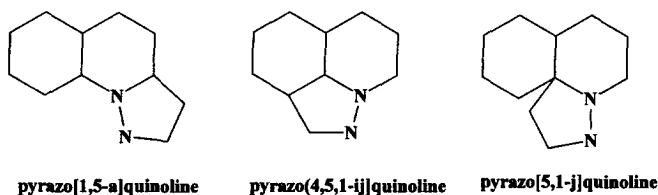
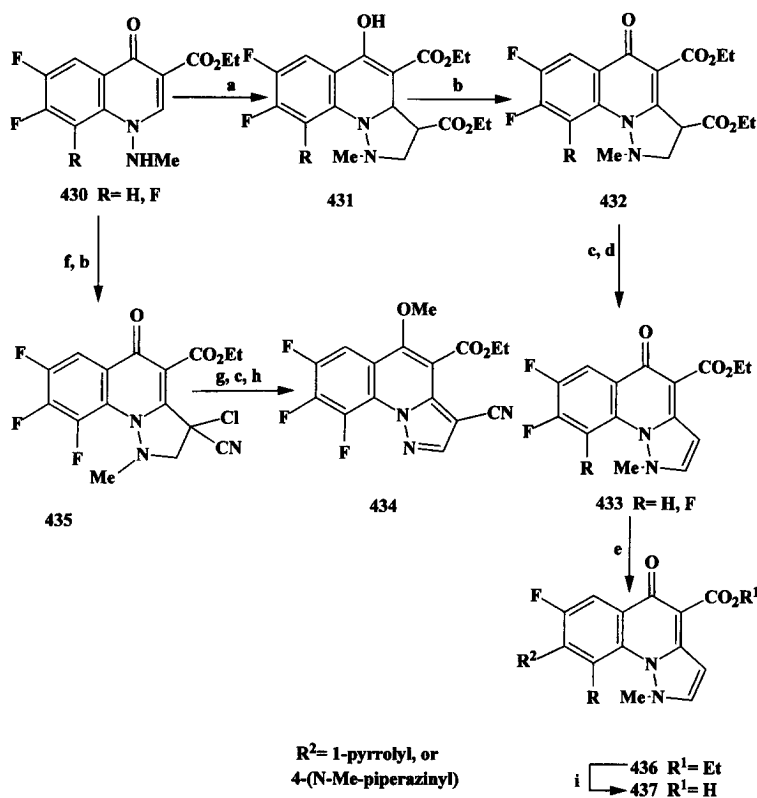


Fig. 5

Reaction of benzaldehyde with 1-amino-2-hydroxymethyltetrahydroquinoline **446** gave **447**, whose oxidation with either the Parikh–Doering method (DMSO,  $\text{SO}_3$ –pyridine complex) or the Swern method [ $\text{DMSO}-(\text{COCl})_2$ ] gave the corresponding aldehyde **448**. Its cyclization was effected by treatment with niobium trichloride–dimethoxyethane complex ( $\text{NbCl}_3$ –DME) in THF to give **449** (93JCS(P1)2087). Alternatively, it was obtained via condensation of ethyl benzoylacetate with 1-amino-2-quinolone **446** to give **450** that followed by base catalyzed cyclization to afford pyrazoquinoline derivatives **449** (84MI215) whose pregnancy termination activity was studied (Scheme 75).

Amination of quinoline with mesitylenesulfonyl hydroxylamine gave *N*-aminomesitylenesulfonate **451** (73T2359) which upon reaction with *p*-toluenesulfonyl chloride gave the *N*-*p*-toluenesulfonylaminoquinolinium ylide **452**. Cycloaddition with acetylene derivatives and subsequent aromatization gave pyrazoquinolines **453** (75JHC119, 82JHC573). On the other hand, treatment of the amination product **451** with  $\text{H}_2\text{NOSO}_3\text{H}$  gave the corresponding dimer that upon reactions with acetylene derivatives gave **453** (77LA506). Reaction of the 1-aminoquinolinium iodide and 2,5-dimethyl-3,4-diphenyl cyclopentadienone gave **454** (54%) and 1,2-adduct (2%). Heating **454** with acetylene derivatives gave **453** (79TL1765). On the other hand, reaction of *N*-iminoquinolinium derivative **451** with perfluoropropene or perfluoro-2-butene, in presence of  $\text{K}_2\text{CO}_3$  in DMF gave the



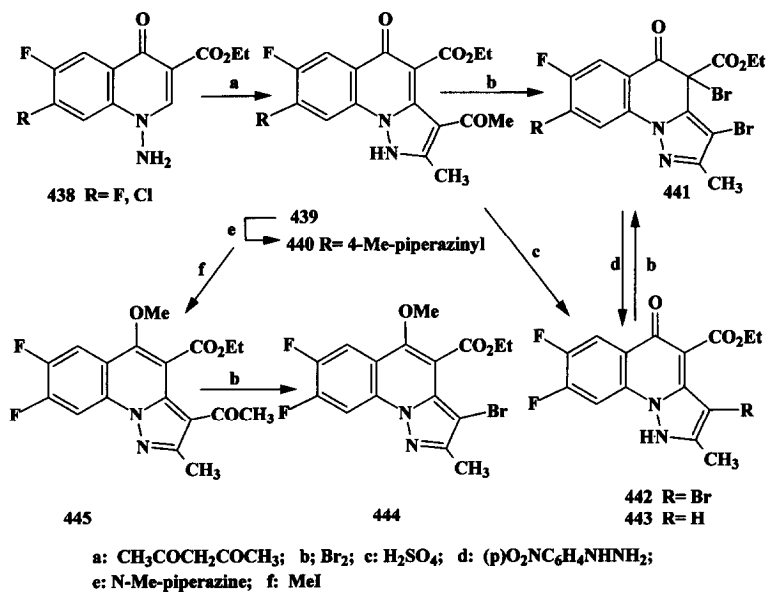


a:  $\text{CH}_2=\text{CHCO}_2\text{Et} / \text{NaH} / \text{DMF} / 0^\circ\text{C}$ ; b:  $\text{DDQ} / \text{C}_6\text{H}_6 / \text{rt}$ ; c:  $6\text{N HCl} / \text{AcOH} / 50^\circ\text{C}$ ;  
d:  $\text{MnO}_2$  or  $\text{DDQ}$ ; e: pyrrole or *N*-Me-piperazine; f:  $\text{H}_2\text{C}=\text{CH}(\text{Cl})\text{CN} / \text{NaH} / \text{DMF}$ ;  
g:  $\text{Et}_3\text{N} / \text{CH}_2\text{Cl}_2 / \text{rt}$ ; h:  $\text{K}_2\text{CO}_3 / \text{MeI} / \text{DMF}$ ; i:  $\text{NaOH}$  or  $\text{HCl}$

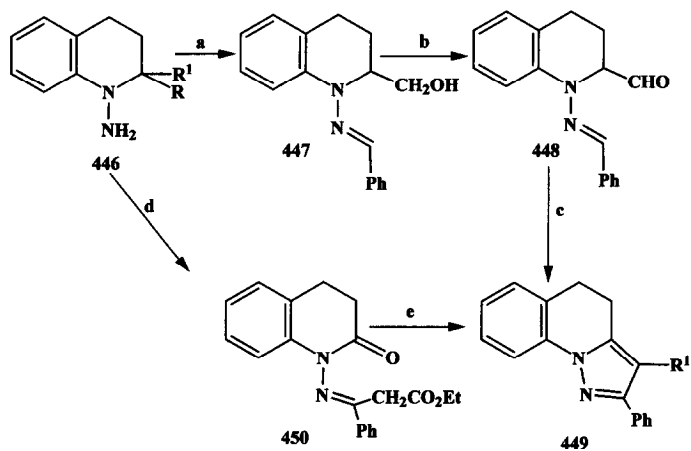
Scheme 73

addition product **455** which gave the pyrazoloquinoline derivatives **456** and **457** upon successive loss of two molecules of HF (82JCS(P1)1593). Reaction of **451** with methoxy substituted ethylene in presence of  $\text{Et}_3\text{N}$  gave **453** ( $R = \text{H}$ ) (90JHC263) (Scheme 76).

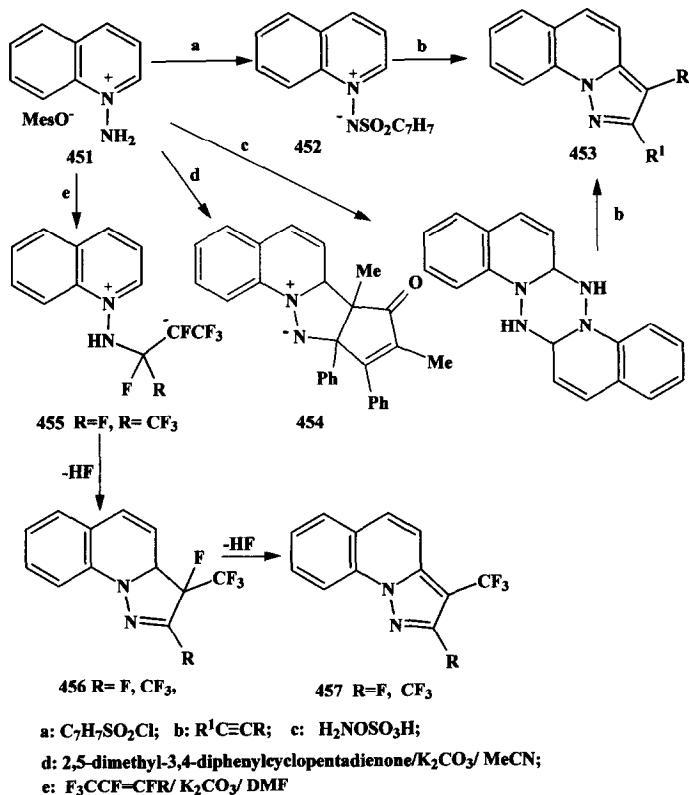
Beckmann rearrangement of the anti-isomer of the ketoximes **458** with *p*-toluene sulfonyl chloride gave the pyrazoquinoline **459**. On the other hand, treatment of **458** with 2,4,6-trimethylbenzenesulfonamide gave **459** regardless of the configuration of the oxime (81LA1751). The conversion of **458** to **459** was found to readily take place upon reaction with mesitylenesulfonyl hydroxylamine (75JHC481). The reaction may take place



Scheme 74



Scheme 75

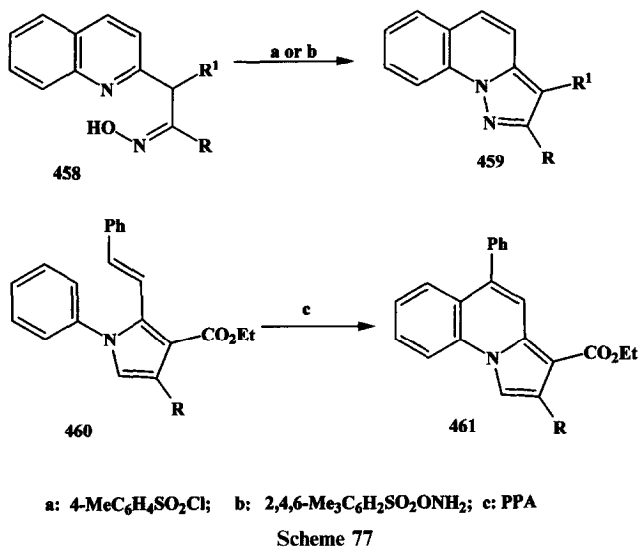


Scheme 76

via the initial formation of N-amine salt from which the hydroxylamine has been eliminated to give the cyclized product. On the other hand, the ketone corresponding to **458** gave a very low yield of **459** under similar reaction condition (75JHC481). A different approach for the synthesis of such ring system utilized the styrylpyrazole **460** which upon cyclization with PPA gave **461** (82S1088) (Scheme 77).

## 2. Pyrazo[4,5,1-ij]quinolines

This tricyclic ring system was prepared from the functionalized pyrazo[1,5-*a*]pyridines. Thus, pyrazo[1,5-*a*]pyridine-3-carboxylate **462** gave **465** upon mesylation and subsequent reaction with 2-ethoxy-2-lithioxyethylene, whose cyclization afforded **466** (94AP435). Intramolecular aldol



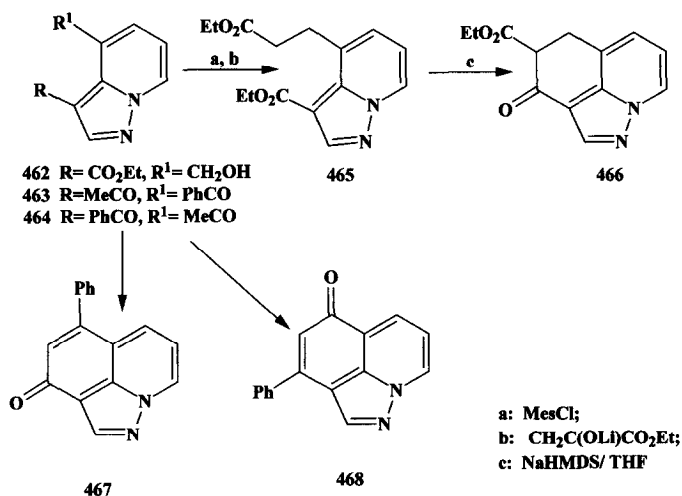
condensation of diacylpyrazopyridine **463** and **464** gave **467** and **468**, respectively (84H2467) (Scheme 78).

## B. IMIDAZOQUINOLINES

There are five possible classes of compounds which can be drawn under this heading of imidazoquinolines. Examples of imidazo[1,2-*a*]quinoline, imidazo[1,5-*a*]quinoline and imidazo[4,5,1-*ij*]quinoline (Fig. 6) are found in literature. The respective isomers having the imidazole ring fused on face *j* are not so far known.

### 1. Imidazo[1,2-*a*]quinolines

Chloroacetylation of 2-amino-4-quinolone **469** gave 2-[bis(chloroacetyl)]amino-4-(chloroacetoxy)-3-phenylquinoline **470** which upon cyclization with KOH gave 1*H*-2,3-dihydro-2,9-dioxo-10-phenylimidazo[1,2-*a*]quinoline **471** (90KG388). Treatment of 2-aminoquinoline with PhCHClCOCO<sub>2</sub>Me in CHCl<sub>3</sub> gave **472** that can be cyclized to the imidazo[1,2-*a*]quinoline **473** (90IZV2627). On the other hand, treatment of 6-chloro-4-phenyl-*N*-glycinylnquinoline with dimethylformamide dimethyl acetal (DMF-DMA) in presence of dicyclohexylcarbodiimide (DCC) afforded 2-dimethylamino-methylene-1,2-dihydroimidazo[1,2-*a*]quinoline-1-one **474** (88CIL94).



Scheme 78

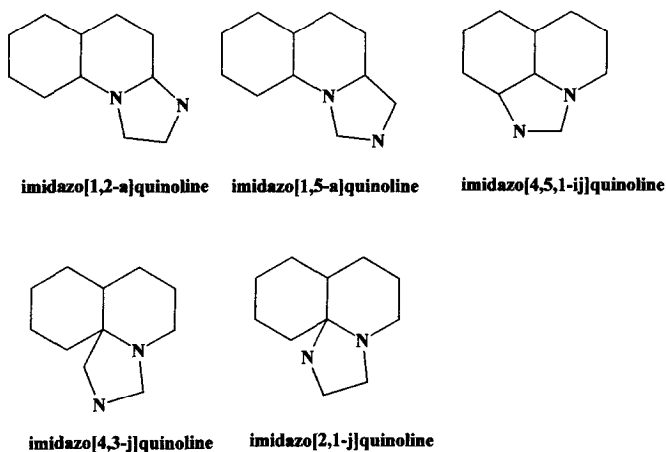
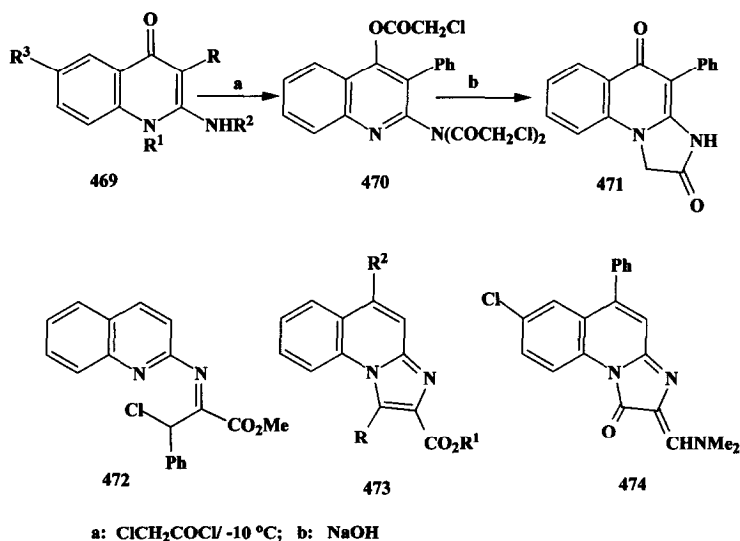


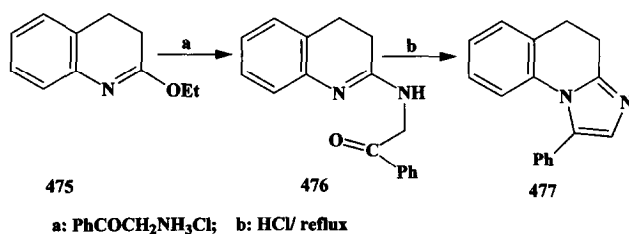
Fig. 6

Reaction of 2-aminoquinoline derivatives with BrCH<sub>2</sub>COCO<sub>2</sub>Et gave imidazoquinoline-2-carboxylate **473** which upon hydrolysis with sodium hydroxide gave the corresponding acid which had been tested against the *passive cutaneous anaphylaxis* (78GEP2802493, 78BEP858605) (Scheme 79).

Substitution of the ethoxy group in the 2-ethoxyquinoline derivative **475** with phenacylammonium chloride afforded 2-phenacylaminoquinoline **476** that upon cyclization with HCl gave **477** (98CHE828) (Scheme 80).

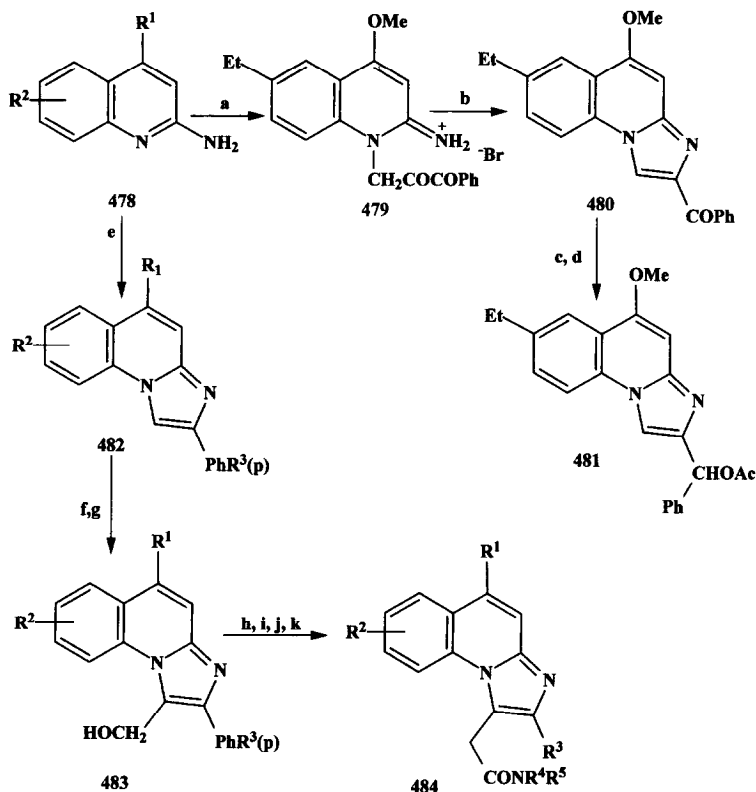


Scheme 79



Scheme 80

Reaction of 2-aminoquinoline **478** with  $BrCH_2COCOPh$  gave the iminium salt **479** which upon reflux in ethanol afforded the imidazoquinoline **480** (82EP62580). Reduction of **480** with sodium borohydride gave the corresponding alcohol which upon esterification with acetyl chloride afforded the ester **481** (84GBP2127824). Heating of **478** with  $\alpha$ -bromo-substituted acetophenones gave **482** which upon formylation and subsequent reduction gave the hydroxymethyl derivatives **483**. Subjecting **483** to tosylation, cyanation, hydrolysis and amidation afforded **484** which were tested for anxiolytic activity (87USP4675323). The 2-(4-chlorophenyl)imidazo[1,2-*a*]quinoline-1-acetamide showed anxiolytic, hypnotic, and anticonvulsant activities (86EP172097) (Scheme 81).

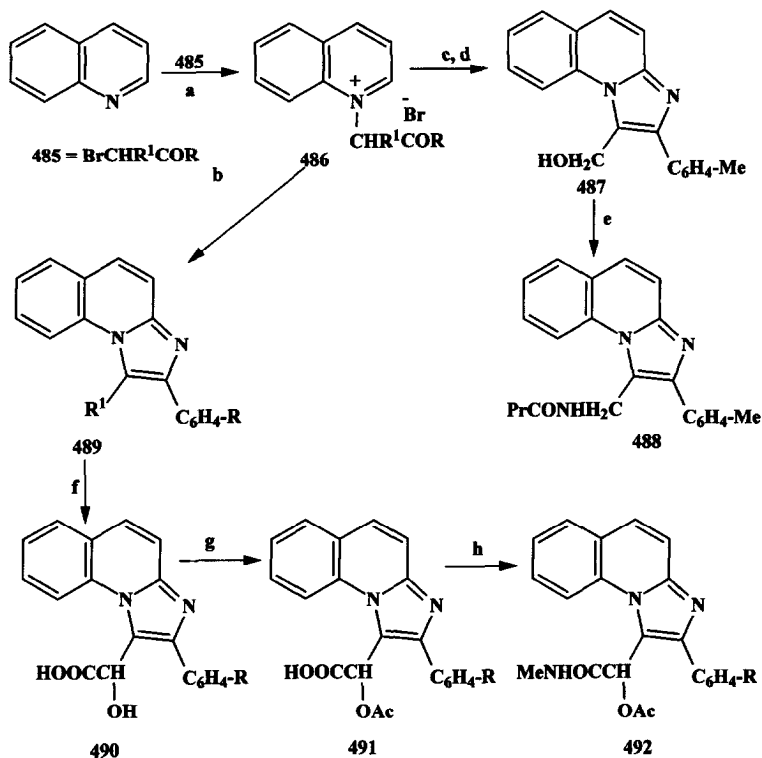


a:  $\text{PhCOCOCH}_2\text{Br}$ ; b:  $\text{EtOH}/\text{reflux}$ ; c:  $\text{NaBH}_4$ ; d:  $\text{AcCl}/\text{Pyridine}$ ;  
 e:  $\text{R}^3\text{COCH}_2\text{Br}/\text{K}_2\text{CO}_3/\text{PrOH}$ ; f:  $\text{DMF}/(\text{COCl})_2$ ; g:  $\text{NaBH}_4$ ; h:  $\text{TsCl}$ ;  
 i:  $\text{NaCN}$ ; j: hydrolysis; k:  $\text{HNR}^4\text{R}^5$

Scheme 81

Heating quinoline with bromoacyl derivatives **485** in  $\text{CH}_2\text{Cl}_2$  gave **486** which upon cyclization with  $\text{NH}_4\text{OAc}$  gave **489**. Reaction of **489** with glycolic acid in  $\text{AcOH}$  afforded **490** which upon esterification with  $\text{AcOH}$  gave **491** that was amidated to afford **492** (87FRP2593179). Cyclization of **486** (87EP231138) afforded the respective imidazoquinoline derivative which upon hydroxymethylation gave the hydroxymethyl derivative **487** that was transformed to the amide **488** (87EP231138) which showed a pregnancy termination activity in mice (91MI251) and inhibit Cardiazol-induced convulsions (87FRP2593179) (Scheme 82).

The imidazole ring can be constructed on the quinoline by reaction with bromomethyl phenacyl hydrazones to afford **493** (91H2373). On the other



a: CH<sub>2</sub>Cl<sub>2</sub>; b: NH<sub>4</sub>OAc; c: AcONH<sub>4</sub>/FeCl<sub>3</sub>/EtCO<sub>2</sub>H; d: HCHO;  
 e: PrCN/H<sub>2</sub>SO<sub>4</sub>; f: HOCH<sub>2</sub>CO<sub>2</sub>H/ AcOH; g: AcOH; h: MeNH<sub>2</sub>

Scheme 82

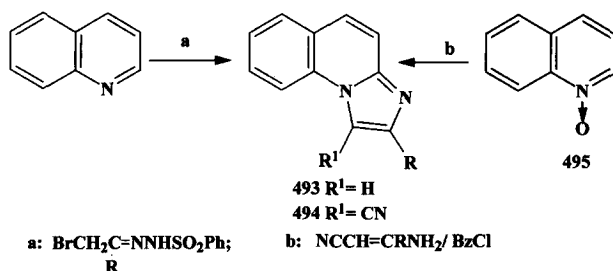
hand, reaction of quinoline-1-oxide **495** with 3-aminocrotononitrile or 3-aminocinnamonitrile in the presence of benzoyl chloride gave **494** (79CPB1004).

The imidazoquinoline derivatives **497** and **498** (84MI1078), were obtained by treatment of nizofenone fumarate **496** with acid (Schemes 83 and 84).

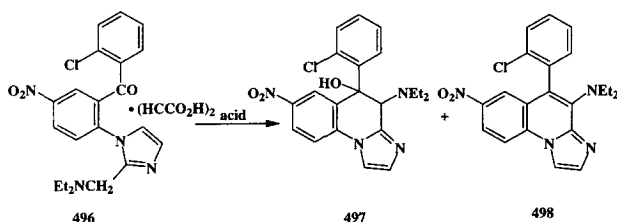
## 2. Imidazo[1,5-a]quinolines

Melting of 2-aminomethyltetrahydroquinolines **499** with urea gave the imidazo derivative **500** that upon alkylation gave **501** (83JHC139). On the other hand, cyclization of **499** with ethyl acetamide hydrochloride gave **502**





Scheme 83



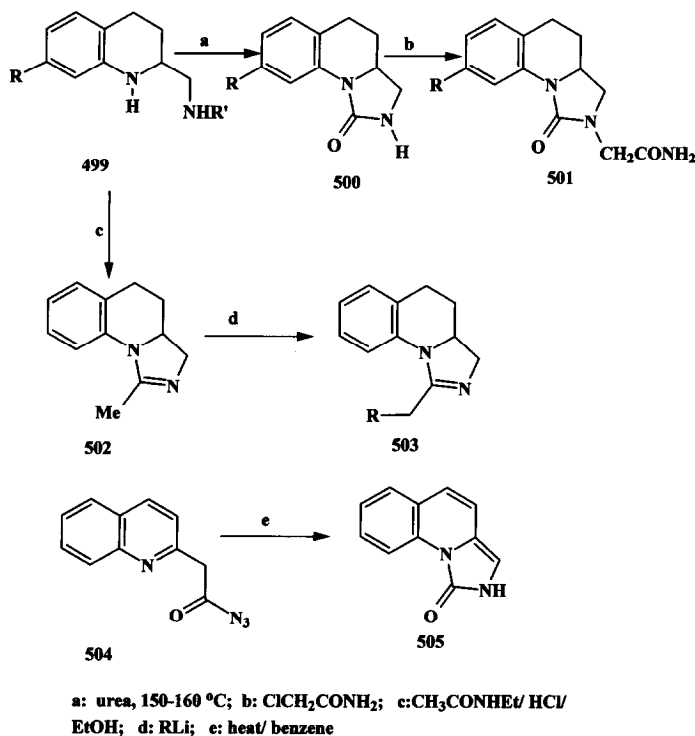
Scheme 84

that can be C-alkylated upon treatment with alkyl lithium to give **503** (90JCS(P1)385). Thermolysis of 2-quinolylacetyl azide **504** gave **505** (79JHC689) (Scheme 85).

Nitrosation of methyl 2-quinolylacetates **506** afforded the corresponding oximes **507** which upon reduction afforded 2-quinolylglycinates **508** that was cyclized by the use of *N,N*-dimethylformamide dimethylacetal to imidazo[1,5-*a*]quinolines **509** (91JHC1715, 91ZN(B)1110). On the other hand, reaction of 2-cyanoquinolines with  $\text{POCl}_3/\text{DMF}$  gave 1-dimethylamino-3-formylimidazo[1,5-*a*]quinoline derivatives **510** (98JCS(P1)3851, 95JAPK07112983) (Scheme 86).

Esterification of the corresponding quinoline-4-carboxylic acid gave the ester **511** which upon reaction with pyrrolidine in THF gave the amide **512**. Its phosphorylation and reaction with **513** in presence of  $\text{KOBu}^t$  afforded **514** which is useful in the treatment of anxiety, sleep disorders, panic states, convulsions, muscle disorders (95WOP9514020) and chronic neurodegenerative diseases (97WOP9700074) (Scheme 87).

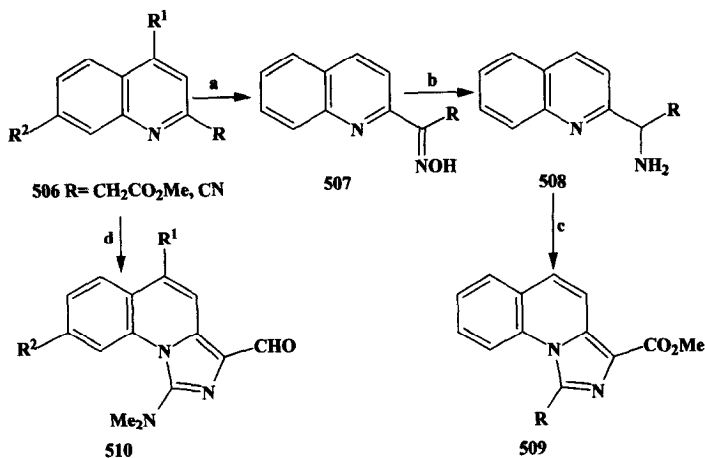
Wittig reaction of 3-nitrophenyltriphenylphosphonium chloride **515** with 4-formylimidazole **516** gave a mixture of the stereoisomers of the respective styrenes together with imidazoquinoline **517** (84CS38) (Scheme 88).



Scheme 85

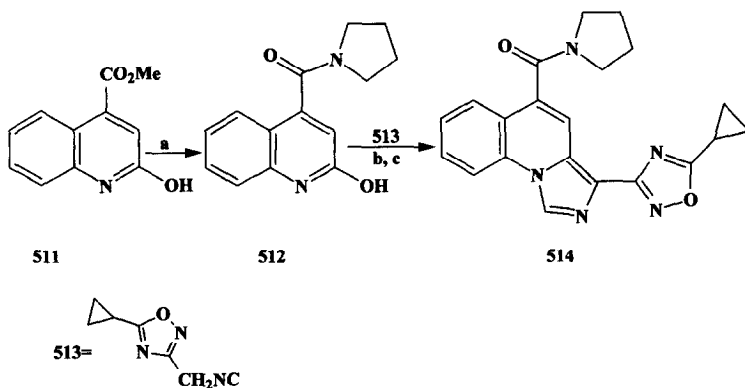
### 3. Imidazo[4,5,1-ij]quinolines

Reduction of quinoline with diisobutylaluminium hydride gave 1,2-dihydroquinoline which was transformed to the corresponding *t*-butoxycarbonyl derivative **518** whose bromination with *N*-bromosuccinimide in DMSO/H<sub>2</sub>O gave the bromohydrin **519** that upon treatment with methylamine afforded **520**. Treatment with triphenylphosphine/diethyl azadicarboxylate gave the aziridine derivative **521**. Catalytic hydrogenation afforded the amine **522** which upon benzylation and introducing an azide group at position 8 followed by reduction gave the amine **523**. Cyclization with KOBu<sup>t</sup> gave the tricyclic imidazoquinoline whose debenzoylation and then formylation gave the formamido derivative which upon reduction with borane-methyl sulfide gave the dimethylamino derivative **524** that show good dopaminergic (D<sub>2</sub>) and serotonergic (5HT<sub>1A</sub>) activities in binding assays (97JMC639). Alternative cyclization can be carried out with 1,1'-carbonyldiimidazole as in the conversion of **525** to **526** (92JMC1076) (Scheme 89).



a:  $\text{NaNO}_2/\text{AcOH}$ ; b:  $\text{Zn}/\text{AcOH}/\text{Ac}_2\text{O}$ ; c:  $\text{DMF-DMA}$ ; d:  $\text{POCl}_3/\text{DMF}$

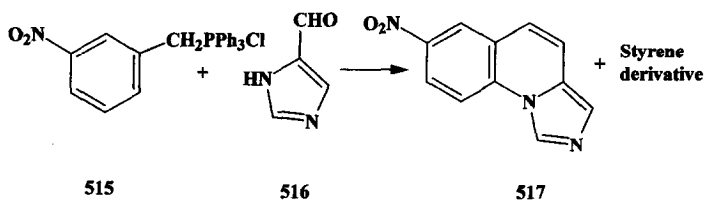
Scheme 86



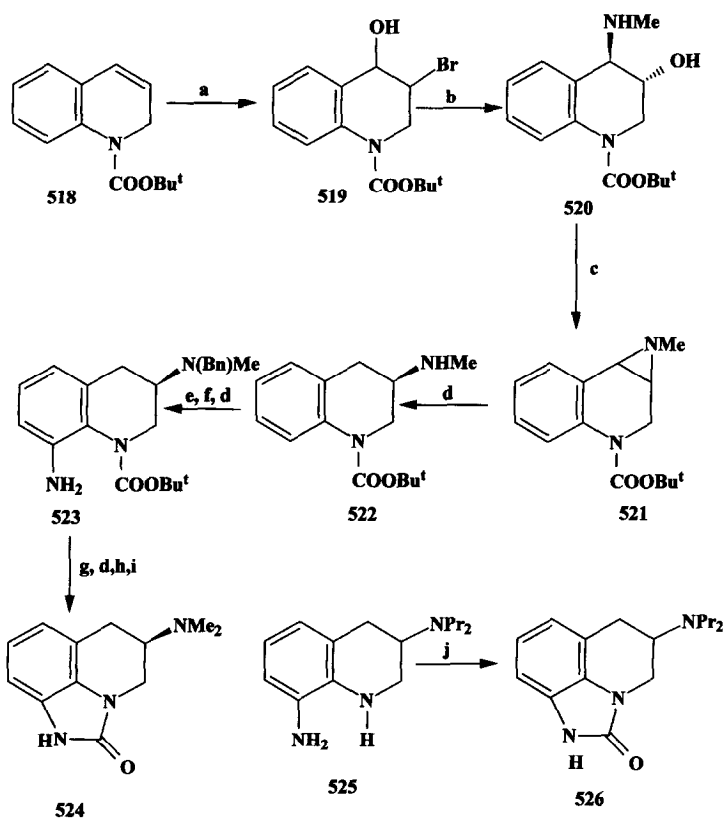
a: pyrrolidine/THF; b:  $\text{KO}^t\text{Bu}$ ; c:  $(\text{EtO})_2\text{POCl}$

Scheme 87

A synthesis for the enantiomerically pure **535** was developed starting with D-phenylalanine which upon reaction with methyl chloroformate gave **528** whose reaction with methoxylamine afforded **529**. Cyclization with bis(trifluoroacetoxy)iodobenzene in presence of trifluoroacetic acid gave the tetrahydroquinoline derivative **530** which was demethoxylated to give **531**. Treatment of **531** with either benzyl chloroformate or

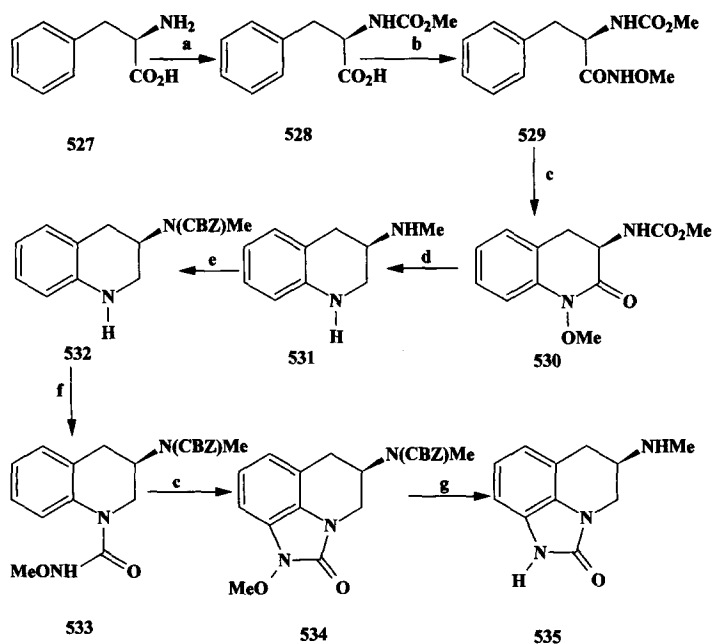


Scheme 88



**a:** NBS/ DMSO/  $H_2O$ ; **b:**  $MeNH_2$ /  $MeOH$ / l-tartaric acid/  $NaOH$ ; **c:**  $Ph_3P$ / DEAD;  
**d:**  $H_2$ /  $Pd-C$ /  $EtOH$ ; **e:**  $BnBr$ ; **f:**  $Bu^tLi$ /  $TsN_3$ ; **g:**  $KOBu^t$ /  $THF$ ; **h:**  $HCOOCOMe$ ;  
**i:**  $BH_3 \cdot Me_2S$ ; **j:** 1,1'-carbonyldiimidazole

Scheme 89



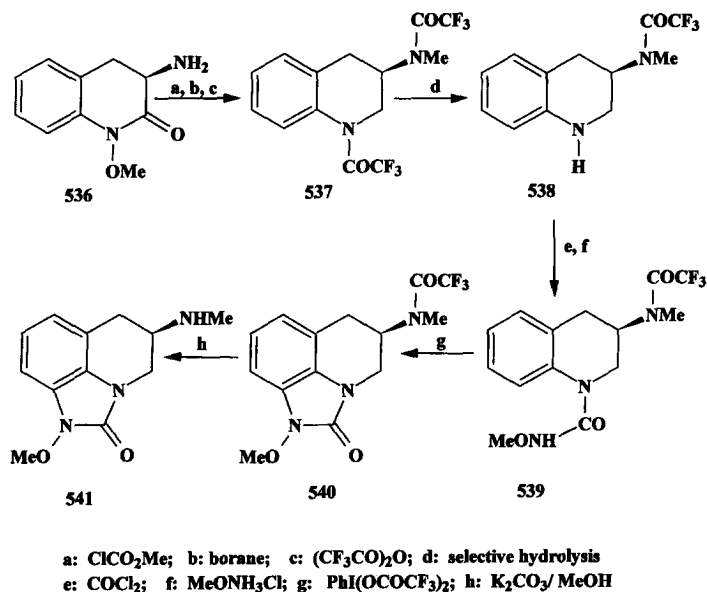
a:  $\text{ClCO}_2\text{Me}$ ; b:  $\text{MeONH}_2/\text{EDC}$ ; c:  $\text{PhI}(\text{O}_2\text{CCF}_3)_2/\text{CF}_3\text{COOH}/\text{CH}_2\text{Cl}_2$ ;

d:  $\text{BH}_3/\text{Me}_2\text{S}/\text{reflux}$ ; e:  $\text{O}-\text{CBZ}$  ; f:  $\text{COCl}_2/\text{MeONH}_2$ ; g:  $\text{H}_2/\text{Pd}(\text{OH})_2-\text{C}$

Scheme 90

*N*-benzyloxycarbonyloxy-succinimide gave **532** whose reaction with phosgene followed by methoxylamine gave the urea derivative **533**. Cyclization with bis(trifluoroacetoxy)iodobenzene-trifluoroacetic acid afforded the imidazoquinoline **534** which was deprotected upon catalytic hydrogenation to give **535** (97JOC6582). This compound is a selective and high-affinity agonist at the dopamine  $\text{D}_2$  receptor subtype and is of interest as a potential agent for the treatment of Parkinsons disease. A labeled analog at C-2 position (96JLCR1087) was prepared. Bromination of **535** followed by reaction with tritium gas gave **535** labeled at C-6 and C-7 positions (96JLCR1087) (Scheme 90).

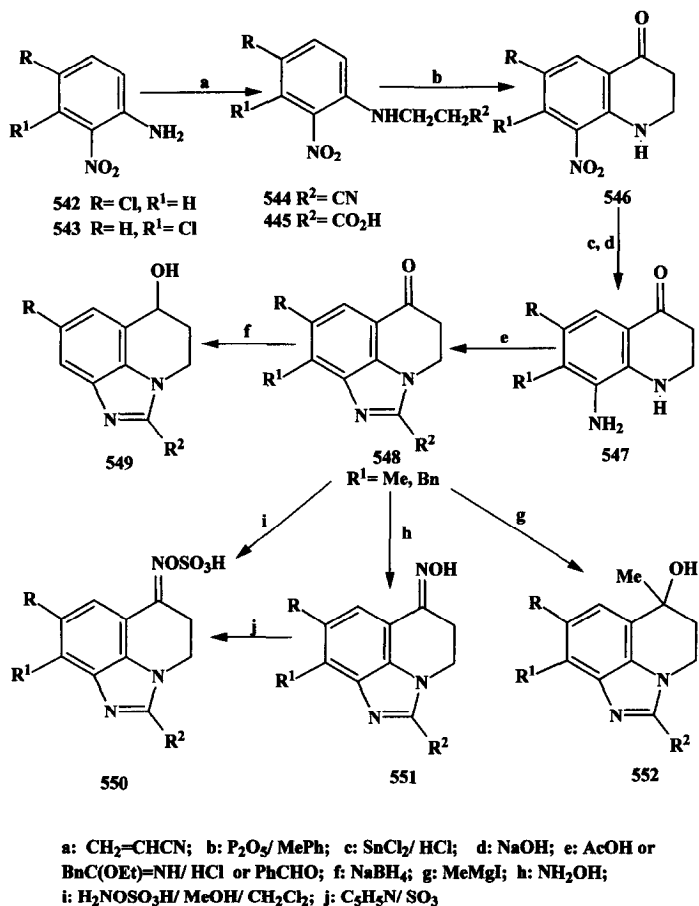
The methoxy derivative **536**, prepared from the aminoquinolone, was transformed into **537**. Selective hydrolysis of **537** gave **538** which was treated with  $\text{COCl}_2$  followed by  $\text{MeONH}_2 \cdot \text{HCl}$  to afford **539** that was cyclized upon treatment with  $\text{PhI}(\text{OCOCF}_3)_2$  to give **540**. Deprotection with  $\text{K}_2\text{CO}_3$  afforded **541** which had central nervous system activity (95WOP9504056) (Scheme 91).



Scheme 91

Reaction of aniline derivative **542** with acrylonitrile gave **544** that was hydrolyzed to the corresponding acid **545** which can also be obtained from the reaction of **543** with acrylic acid. Subsequent cyclization of **543** gave the quinolone **546** whose reduction afforded the amino derivative **547**. Cyclization of **547** gave the imidazoquinoline **548**. Reaction of **548** with  $\text{NaBH}_4$  gave the alcohol **549**, and with hydroxylamine gave the oxime **551**, while  $\text{MeMgI}$  gave **552**. Compound **551** had analgesic activity much weaker than aspirin and **548** ( $\text{R} = \text{Bn}$ ) had local anesthetic activity much weaker than cocaine (77MI471). Reaction of **548** with  $\text{NH}_2\text{OSO}_3\text{H}$  gave the oxime derivative **550** which was also prepared from the oxime **551**. By treatment with sulfur trioxide in pyridine, compound **550** gave the potassium salt upon treatment with  $\text{K}_2\text{CO}_3$  (98MI763) which showed diuretic activity and increase of urine output in dog and a drop in blood pressure in mice (91EP405442, 98MI763) (Scheme 92).

Treatment of aniline derivative **553** with methyl acetylenedicarboxylate afforded the enamine **555** which upon cyclization with PPA or thermally gave the quinolinone derivative **556**. Catalytic hydrogenation using  $\text{Pd-C}$  in methanol gave the corresponding amine that upon reaction with ethyl orthoformate gave imidazoquinoline carboxylate **557**. Reaction of **554** with ethoxymethylene malonate gave **561** which upon thermal cyclization gave **560**. Hydrogenation and subsequent reaction with ethyl



Scheme 92

orthoformate or orthoacetate afforded **558** and **559**, respectively (85JMC298) (Scheme 93).

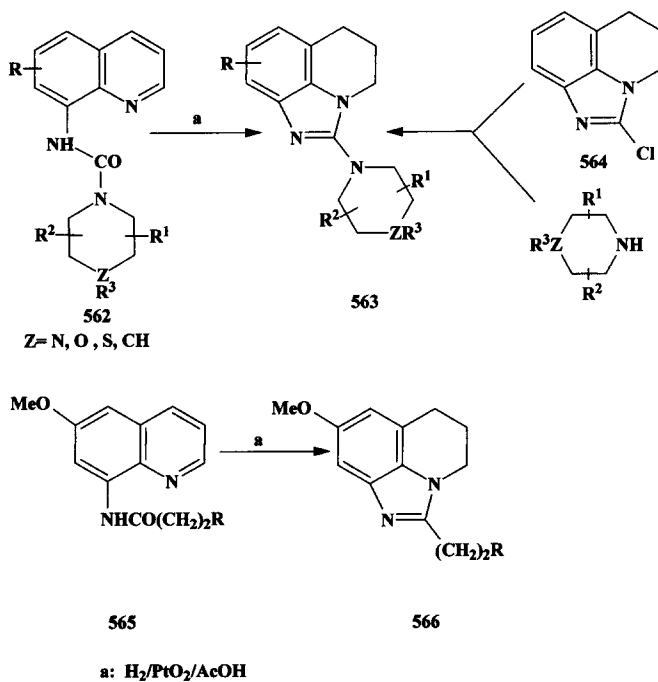
Reductive cyclization of 4-piperidinecarboxamide **562** afforded **563** which could be alternatively obtained by condensation of **564** with the respective cyclic amine. Compound **563** showed inhibition of writhing in mice (96EP700913). Similarly, **565** gave **566** (76JMC1111) (Scheme 94).

Reaction of 8-aminoquinoline **567** with 3,4-dichlorodithiazolium chloride gave the quinolyl iminodithiazole **568** whose thermal rearrangement gave **569** via a molecular rearrangement process (96MI2775) (Scheme 95).

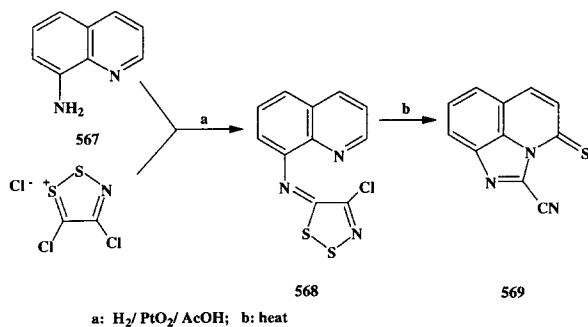
The carbamates, derived from the reaction of 8-aminoquinoline with phenyl or ethyl chloroformate, upon reduction with NaBH<sub>4</sub> gave the





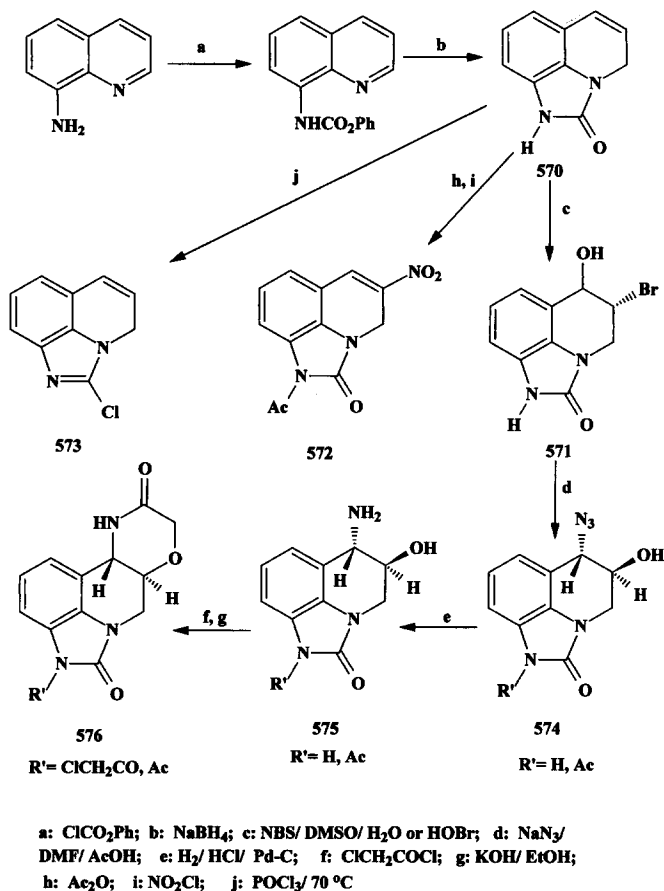


Scheme 94



Scheme 95

(84AP951). Alternatively, reduction of the ester in **586** gave the alcohol **587** that upon reaction with carbon tetrabromide/triphenylphosphine gave the respective bromide which was cyclized under the reaction condition to give **588** (92JMC1076) (Scheme 98).



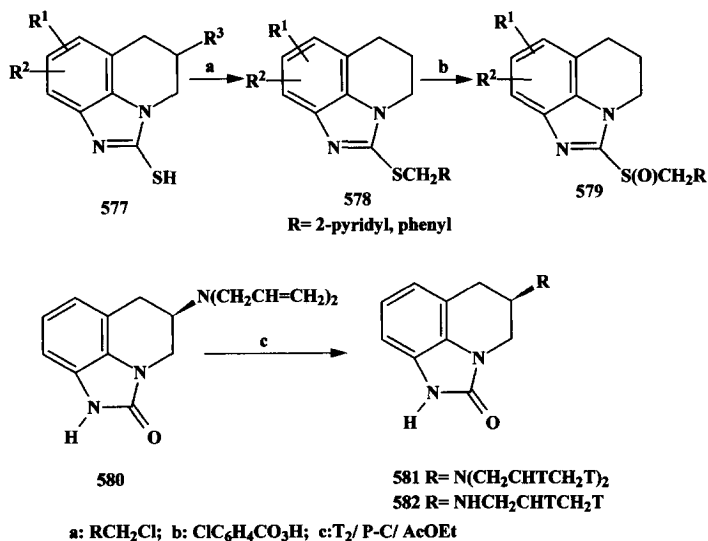
Scheme 96

### C. OXAZOLOQUINOLINES

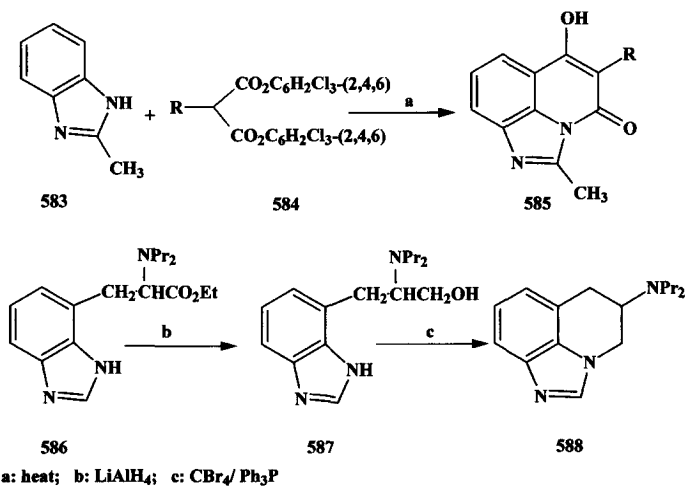
There are eight possible combinations of heteroatoms in that tricyclic system of oxazoloquinoline. However, examples of four of them only are reported in literature (Fig. 7).

#### 1. Oxazolo[3,2-a]quinolines

The oxazole ring can be constructed on a quinoline ring such as **589** by alkylation to give **590** which upon treatment with halogen in  $\text{CHCl}_3$  gave the corresponding oxazoloquinolinium derivative **591** that upon treatment with



Scheme 97



Scheme 98

aqueous alkali afforded **592** (89AKZ636, 91MI120). Halocyclization of 4-methyl-1-vinyl-2-quinolone **594** with bromine in  $\text{CCl}_4$  or  $\text{I}_2$  in alcohol gave the oxazoloquinolinium halide **593** (91MI104). On the other hand, cyclization of 2-allyloxyquinolines **595** with bromine gave the corresponding oxazoloquinolinium bromide **596** (96KG1252) (Scheme 99).

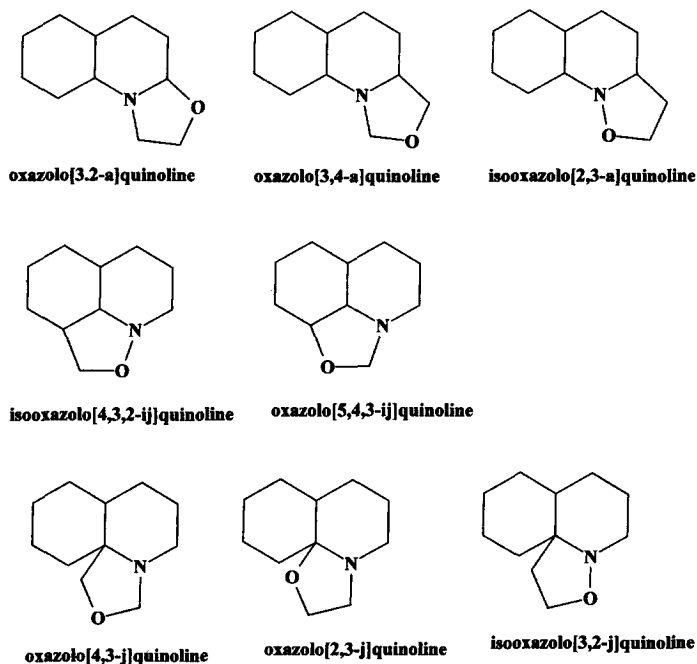


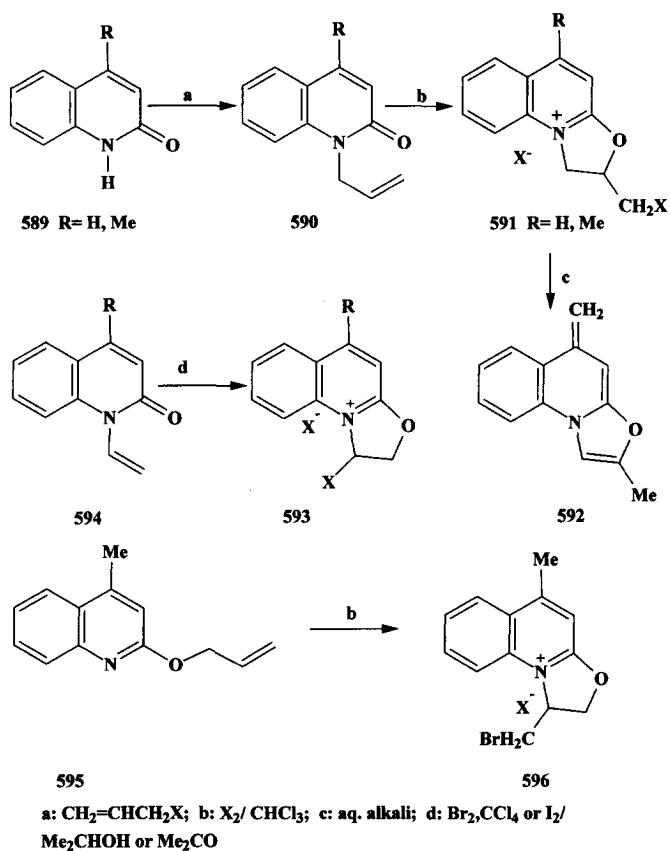
Fig. 7

Treatment of quinoline with ethylene oxide gave oxazolo[3,2-*a*]quinoline **597** whereas 2-methylquinoline did not react with ethylene oxide (79JOC285). The oxazolidine **597** is labile as monitored by  $^1\text{H}$  NMR spectroscopy; its colorless solution in  $\text{CDCl}_3$  became dark red within several hours (Scheme 100).

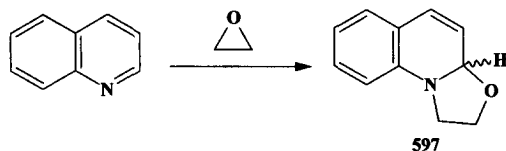
Reaction of 4-hydroxyquinoline-2-one **598** with oxalyl chloride gave oxazoloquinoline **599** (97OPP211). The oxazoloquinoline **600** was obtained as a byproduct during the synthesis of pyranoquinoline alkaloids **601** by reaction of **598** with 2-methyl-2-chlorobutynone under phase transfer catalysis (87JHC869) (Scheme 101).

Reaction of the chiral piperidine derivative **602** with the activated alkyne **603** afforded the corresponding oxazoloquinoline derivative **604** (98H747) (Scheme 102).

The oxazoloquinolinequinone derivative **610** was prepared from the allylphenol **605** which was transformed to the alcohol **606** and then to the aldehyde **607**. Subsequent debenzoylation gave **608** that was oxidized with  $\text{Ce}(\text{NH}_4)_2(\text{NO}_2)_6$  to the quinone **609** that upon cyclization with ethanolamine gave the oxazoloquinolinequinone **610** which showed



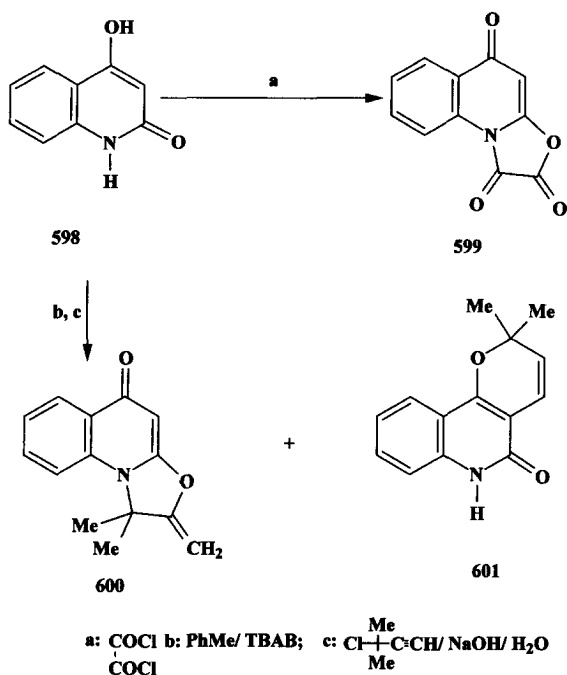
Scheme 99



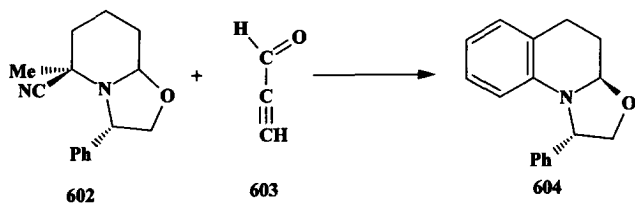
Scheme 100

antitumor activity against culture colon 26 cell (91JAPK03109388) (Scheme 103).

Double cyclization of the phenylglycine *o*-carboxylic acids **611** ( $\text{R}^1 = \text{H}$ ) with acetic or benzoic anhydride by heating gave the mesoionic oxazolones **612** and **613**, respectively, which upon treatment with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  gave **615**



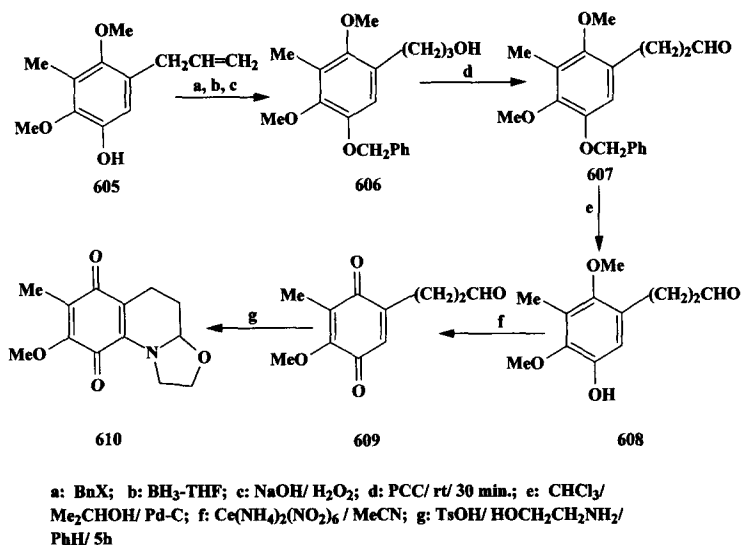
Scheme 101



Scheme 102

that upon tosylation or benzylation gave **614** or **613**. Reaction of trifluoroacetic anhydride with **611** or **612** gave the respective trifluoroacetyl derivatives **616** and **617** (78TL1887, 80T1385). On the other hand, when **611** ( $\text{R}^1 = \text{Me}$ ) was heated with  $\text{Ac}_2\text{O}$  gave the oxazoloquinoline **618** instead of the mesoionic product (80T1385). Reaction of aniline with **612** gave quantitatively 4-anilino-2-quinoline-*N*-acetic acid derivative **619**, probably via **615** (Scheme 104).

Reaction of the mesoionic oxazolone **620** with acetylenedicarboxylic ester **621** gave the cycloadduct **622** in aprotic solvents and the Michael adducts



Scheme 103

**623** in protic solvents (78TL1887, 92RRC1307). Reaction of **622** with acetic acid gave **624** (Scheme 105).

## 2. Oxazolo[3,4-*a*]quinolines

Treatment of **625** with acetic anhydride/sodium acetate gave a mixture of the stereoisomers **626** and **627** where the former is the major one (79JCS(P1)1013, 79JHC1589). Their X-ray crystallography confirmed their structure (79JCS(P1)1013) (Scheme 106).

The oxazoloquinoline **629** was obtained from 7-formyloxazoloquinoline **628** as shown in Scheme 107. The inhibition of monamine oxidase by **629** was studied (97FRP2737206).

## 3. Oxazolo[5,4,3-*ij*]quinolines

Thermal cyclization of the arylaminomethylenemalonate afforded quinoline 3-carboxylate **630** whose reaction with 1,1-dibromoethane gave oxazolo[5,4,3-*ij*]quinoline **631**. Acid hydrolysis and reaction with *N*-methylpiperazine gave **632** whose bactericidal activity is superior to that of pipemidic acid (82JAPK57203085) (Scheme 108).

Condensation of the 2-quinolone **633** with ethyl 3-chloroacrylate gave the oxazole derivative **634** (79YZ813). Cyclization of **635** with 1,1'-carbonyldiimidazole gave **636** (92JMC1076) (Scheme 109).

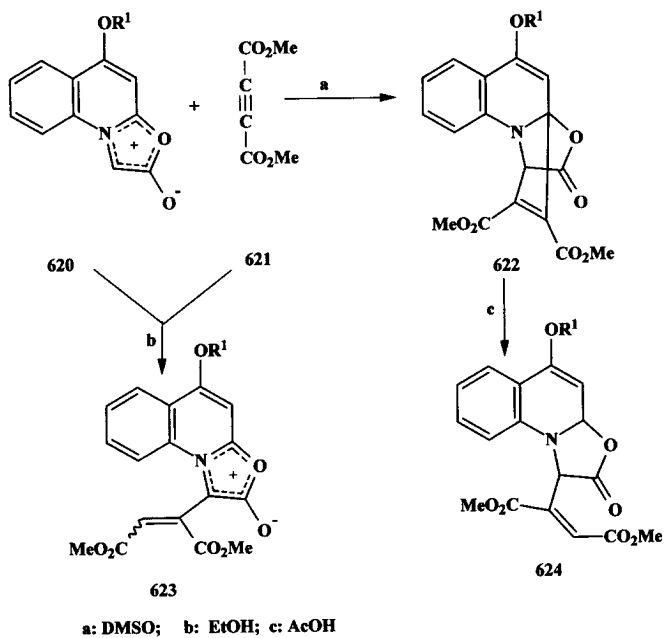


Cyclocondensation of **637** with ethanolamine gave the benzoxazoloquinoline **638a** (83KG1664). Flash vacuum pyrolysis of **639** gave **638b** (93JCS(CC)794) (Scheme 110).

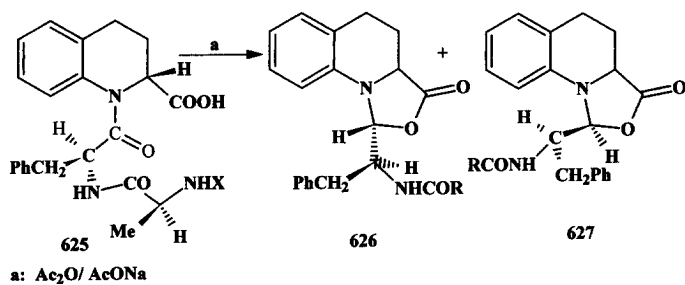
Similar number of the isomeric structures for thiazoloquinolines to that of the oxazoloquinolines can be drawn, but the reported examples for these isomers belong to only three ring systems: thiazolo[3,2-*a*]quinoline, thiazolo[4,3-*a*]quinoline and thiazolo[5,4,3-*ij*]quinoline (Fig. 8).

Quinoline 2-thiols are excellent precursors for construction of this ring system. Thus, allylation or vinylation of quinoline thiol **640** gave 2-vinylthioquinolines **641** or 2-allylthioquinolines **642** which were

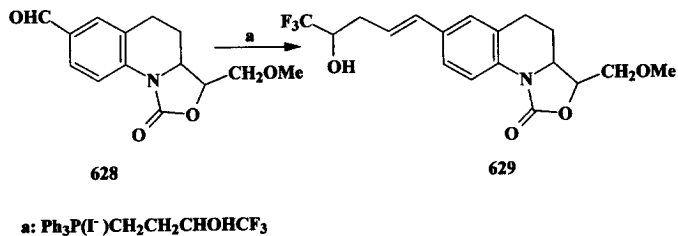




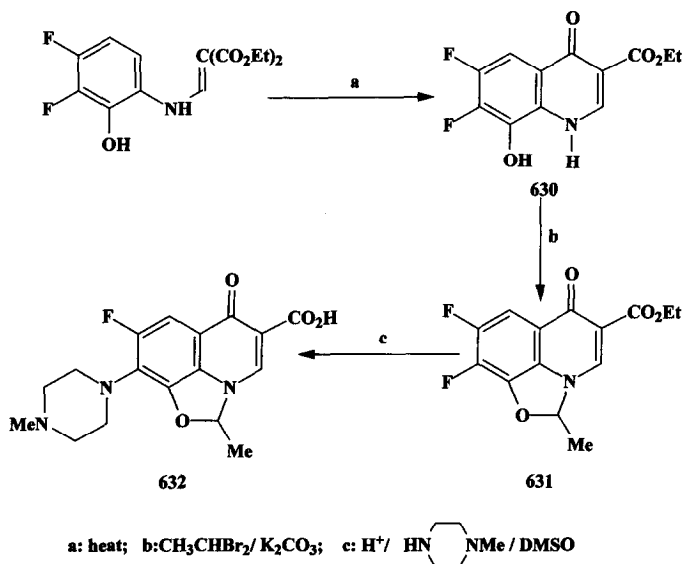
Scheme 105



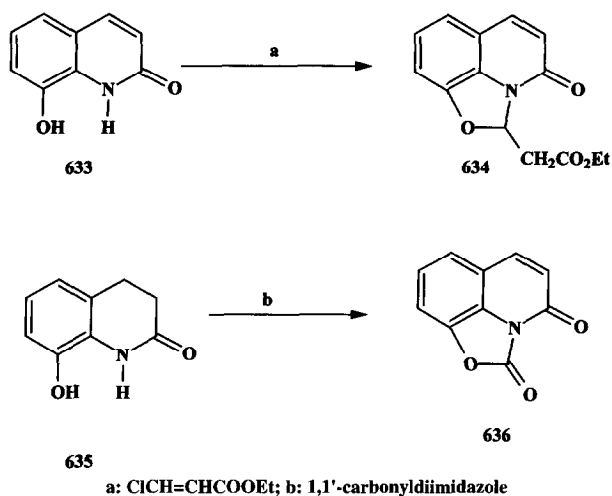
Scheme 106



Scheme 107

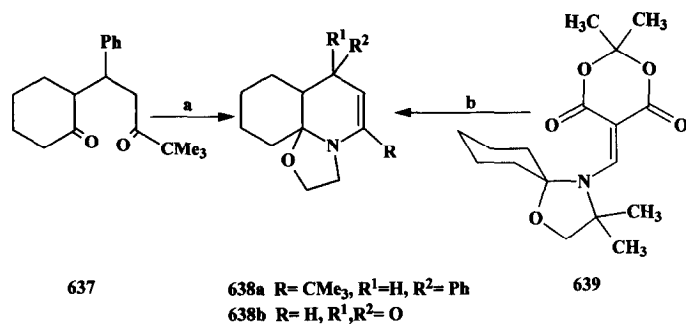


Scheme 108



Scheme 109

cyclized by reaction with bromine in carbon tetrachloride, chloroform or benzene to give the corresponding dihydrothiazolo[3,2-*a*]quinolinium halides **643** and **644**, respectively (87KG690, 81SUP854930, 96KG1252) (Scheme 111).



a:  $\text{HOCH}_2\text{CH}_2\text{NH}_2$ ; b: pyrolysis

Scheme 110

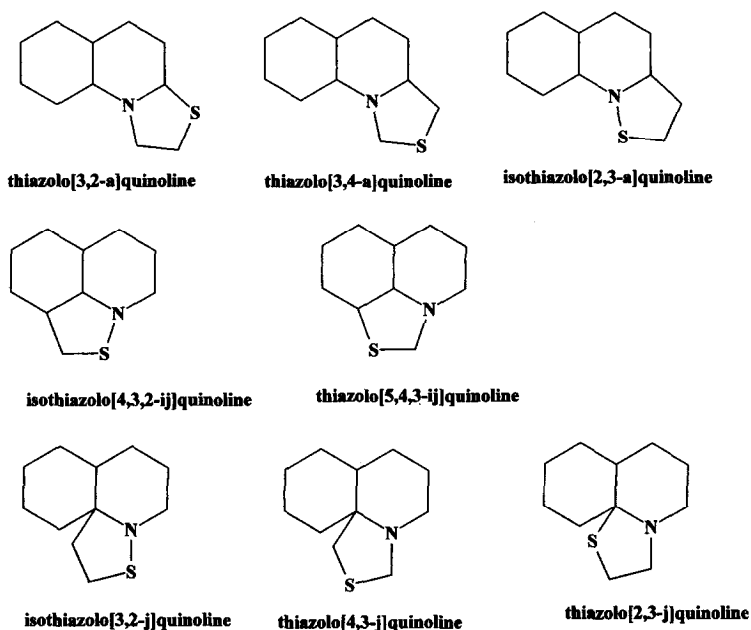
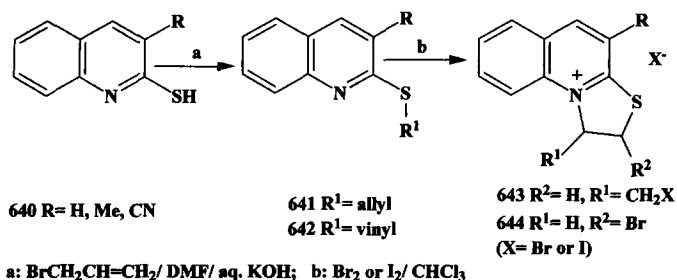
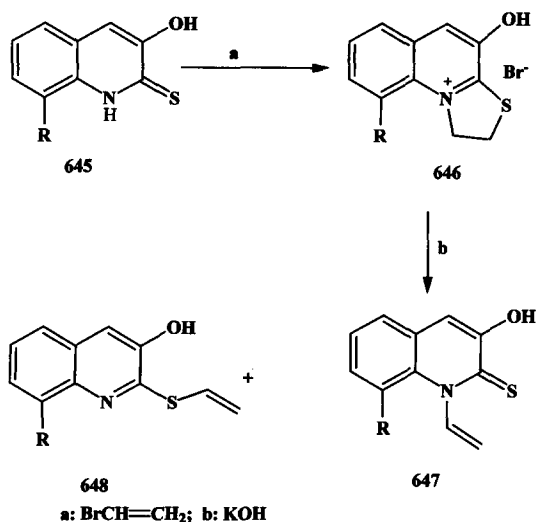


Fig. 8

On the other hand, 3-hydroxyquinoline-2(1*H*)-thiones **645** (readily available from the corresponding isatins) were converted into 1,2-dihydrothiazolo[3,2-*a*]quinolinium-4-olate **646**. Ring opening of **646** gave the *N*- and *S*-vinyl derivatives **647** and **648**, respectively (84ACSA(B)109) (Scheme 112).

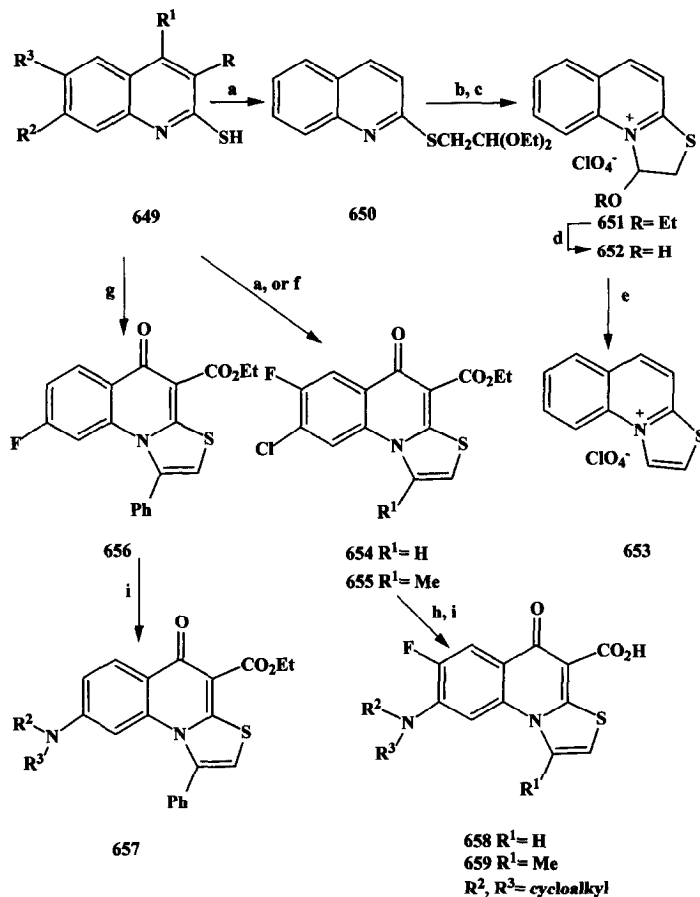


Scheme 111



Scheme 112

Reaction of 2-quinolinethiol **649** ( $R, R^1, R^2, R^3 = \text{H}$ ) with bromoacetaldehyde diethyl acetal gave 2-(2-quinolythio)acetaldehyde diethylacetal **650** which was cyclized by standing at room temperature with 6 N HCl and isolated as ethoxythiazolo[3,2-*a*]quinolinium perchlorate derivative **651**. Heating **651** with 6 N HCl gave the corresponding 1-hydroxy derivative **652** which could be acetylated. Dehydration of **652** with  $\text{H}_2\text{SO}_4$  followed by  $\text{HClO}_4$  gave **653** (99JHC937). Refluxing appropriate derivatives of 2-mercaptoquinoline **649** with phenacyl bromide in ethanol, followed by trifluoromethylsulfonic acid gave thiazolo[3,2-*a*]quinolines **656** that upon treatment with saturated heterocycles such as morpholine afforded **657** (89WOP8912055) which showed activity against human colon cancer DLD-1 cell (89WOP8912055, 92JHC1117). On the other hand, reaction of

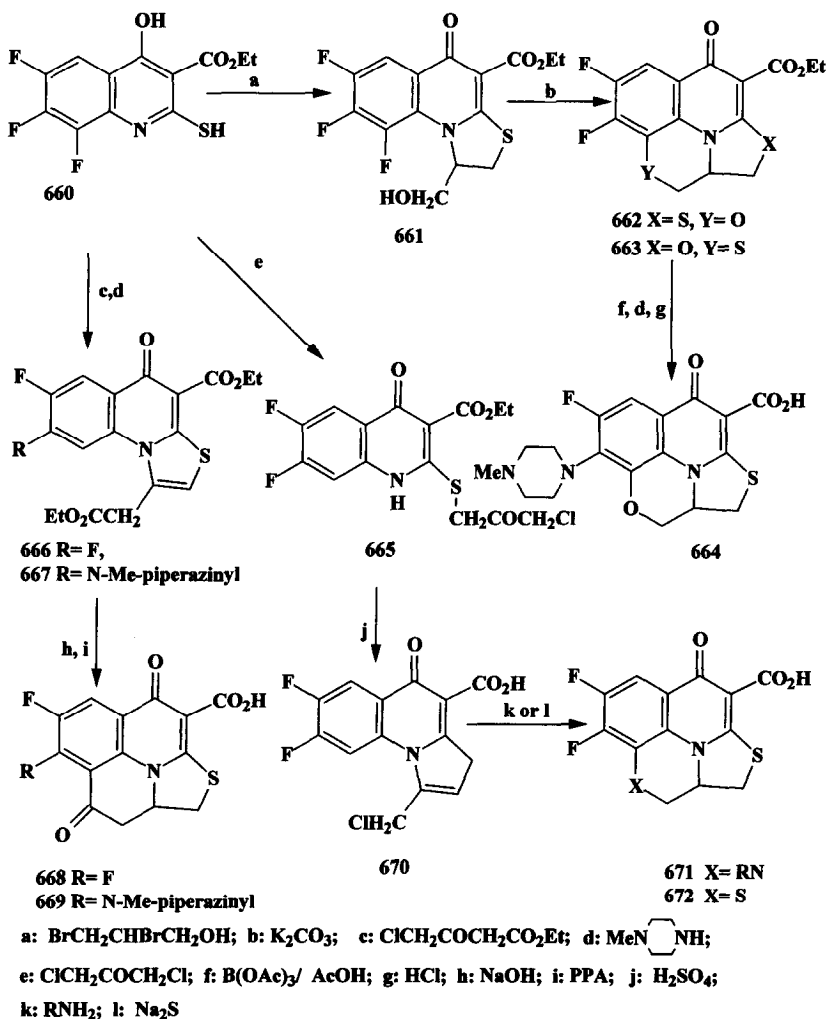


a:  $\text{BrCH}_2\text{CH}(\text{OEt})_2 / \text{K}_2\text{CO}_3$ ; b:  $6\text{N HCl} / \text{rt } 6 \text{ h}$ ; c:  $\text{HClO}_4$ ; d:  $6\text{N HCl} / \text{reflux } 18 \text{ h}$ ; e:  $\text{H}_2\text{SO}_4 / \text{HClO}_4$ ; f:  $\text{ClCH}_2\text{COMe} / \text{K}_2\text{CO}_3$ ; g:  $\text{PhCOCH}_2\text{Br} / \text{reflux} / \text{CF}_3\text{SO}_3\text{H}$ ; h:  $\text{H}_2\text{SO}_4$ ; i:  $\text{N-heterocycles}$

Scheme 113

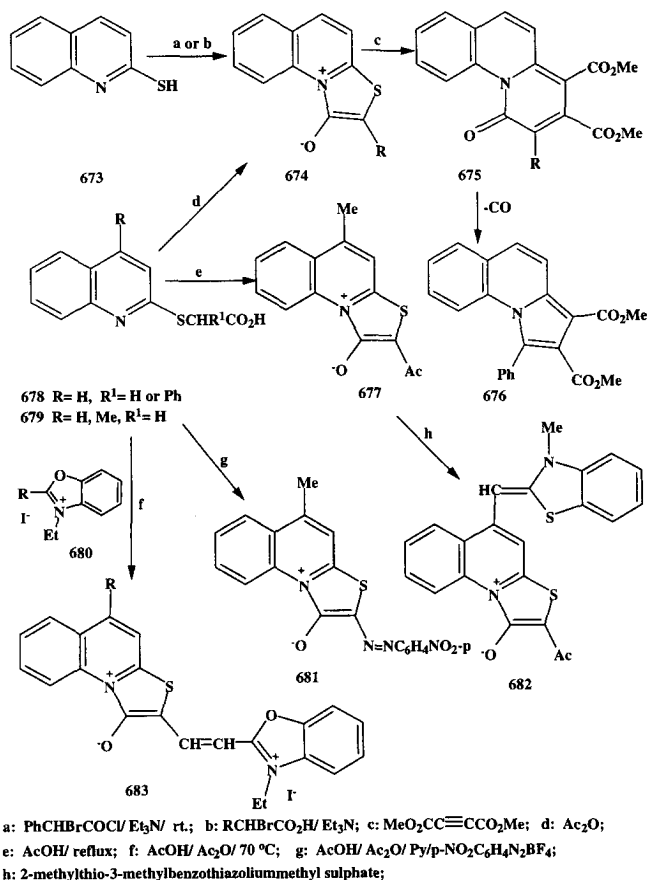
2-mercaptoquinoline-3-carboxylates **649** with bromoacetal or chloroacetone in presence of  $\text{K}_2\text{CO}_3$  gave thiazoloquinoline carboxylates **654** and **655**, respectively that upon saponification and reaction with *N*-methylpiperazine gave the corresponding 8-piperazinyl derivatives **658** and **659** which were tested as antibacterial agents (87USP4659734, 92JHC1117) (Scheme 113).

Treatment of quinoline 2-thiol derivative **660** with 2,3-dibromopropanol gave the thiazoloquinoline **661** which upon treatment with  $\text{K}_2\text{CO}_3$  gave a mixture of **662** and the rearrangement product **663**. Separation, hydrolysis and reaction of **662** with *N*-methylpiperazine afforded **664** (93JMC3148)



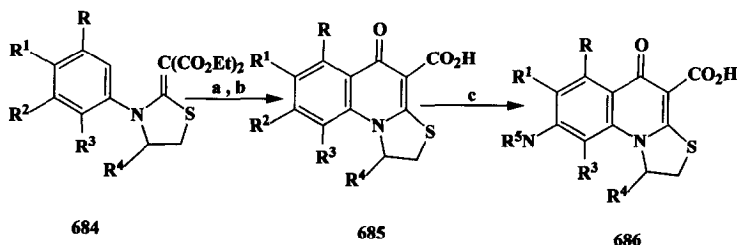
Scheme 114

that was tested against *E. coli* KC-14 (88EP286089). Alternatively, reaction of **660** with 1,3-dichloroacetone gave **665** which upon cyclization with  $\text{H}_2\text{SO}_4$  gave the chloromethyl derivative **670**. Treatment with either  $\text{RNH}_2$  or  $\text{Na}_2\text{S}$  afforded the tetracyclic products **671** or **672**, respectively. On the other hand, reaction of **660** with  $\text{ClCH}_2\text{COCH}_2\text{CO}_2\text{Et}$  gave **666** which upon treatment with  $\text{B(OAc)}_3$  followed by *N*-methylpiperazine gave **667**. Alkaline hydrolysis of **666** or **667** with  $\text{NaOH}$  followed by heating with  $\text{PPA}$  gave **668** and **669**, respectively (93JMC2621) (Scheme 114).



### Scheme 115

Cyclodehydration of 2-mercaptoquinoline **673** with bromoacetic acid or  $\alpha$ -bromo- $\alpha$ -phenylacetyl chloride gave **678** which with acetic anhydride gave anhydro-1-hydroxythiazolo[3,2-*a*]quinolinium hydroxide **674**. Reaction of **674** with acetylene dicarboxylate gave **675** which gave **676** by losing CO (78JOC2700). On the other hand, heating of **679** in acetic acid gave **677** whose reaction with 2-methylthio-3-methylbenzothiazolium methyl sulfate gave **682** (79KG989). The cyclization carried out in acetic acid in presence of pyridine and *p*-nitrobenzenediazonium tetrafluoroborate gave **681** (80KG621). Heating a mixture of 2-(quinolythio)acetic acid **679** with the benzoxazolium iodide **680** in acetic acid followed by addition of acetic anhydride and heating gave the mesoionic compound **683** (81KG481) (Scheme 115).



a: PPA; b: hydrolysis; c: N-Methylpiperazine or 3-aminopyrrolidine

Scheme 116

Cyclization of the thiazolidine methylidinemalonate **684** with PPA gave thiazoloquinoline 3-carboxylate which upon hydrolysis afforded **685** and reaction with *N*-methylpiperazine or a pyrrolidine derivative gave **686** as antibacterial agent (82EP58392, 85USP4550104). (Scheme 116).

Aroylation of 2-cyanomethylthiazole **687** with pentafluorobenzoyl chloride **688** gave the corresponding 2-(benzoylcyanomethyl)thiazole **689** which, via tautomerization to the enamine form, was cyclized to the thiazoloquinoline **690**. Heating **690** with  $\text{H}_2\text{SO}_4$  gave **691** which upon treatment with  $\text{P}_2\text{S}_5$  gave the corresponding thione **692** (88UKZ295) (Scheme 117).

## 2. Thiazolo[3,4-a]quinolines

The only example of this ring system to the best of our knowledge was formed by reaction of  $\text{Me}_3\text{SiCH}_2\text{SCH}_2\text{Cl}$  with quinoline to give the onium salt **693** which upon treatment with  $\text{CsF}$  in  $\text{MeCN}$  at room temperature afforded the thiazoloquinoline **694** (87JOC4423) (Scheme 118).

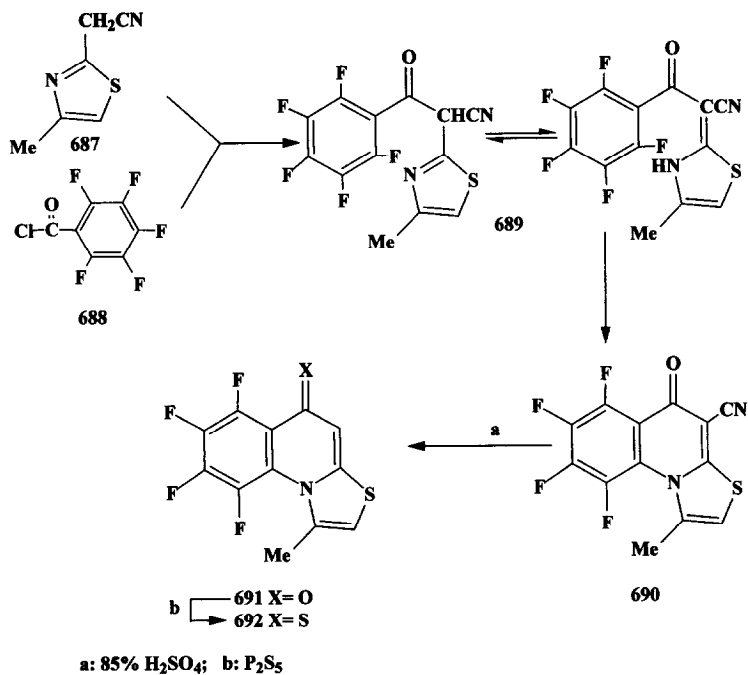
## 3. Thiazolo[5,4,3-ij]quinolines

Reaction of 8-mercaptoquinoline **695** with  $\text{CH}_2\text{I}_2$  gave the thiazoloquinoline **696**. On the other hand, the reaction with the sodium salt of **695** did not give **696** but gave bis(8-quinolythio)methane **697** (93MI107) (Scheme 119).

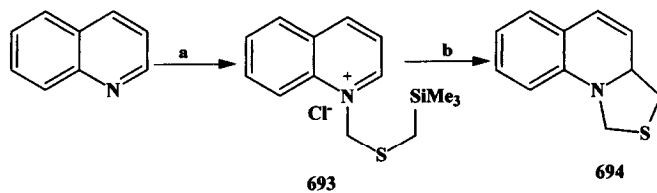
Intramolecular cyclization of benzothiazole derivative **698** by a Claisen self-condensation afforded **699** (81JHC1273) (Scheme 120).

Reaction of 2-aminobenzyl alcohol with butenesulfonyl chloride gave **700** which upon treatment with  $\text{BuLi}$  followed by  $\text{COCl}_2$  gave the benzoxazine **701**. Thermolysis of **701** in 1,2,4-trifluorobenzene gave the thiazoloquinoline **702** (96JCS(P1)1809) via an intramolecular Diels-Alder reaction (Scheme 121).



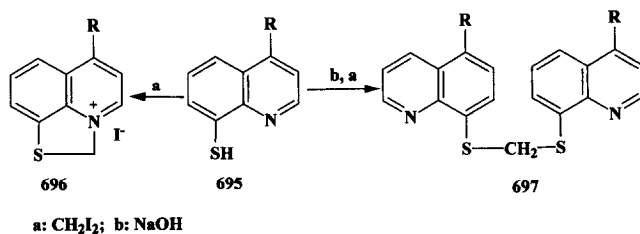


Scheme 117

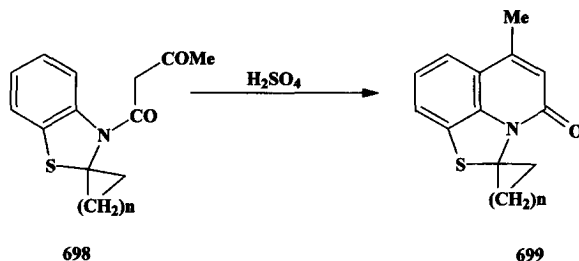


a:  $\text{Me}_3\text{SiCH}_2\text{SCH}_2\text{Cl}$  /  $0^\circ\text{C}$ ; b:  $\text{CsF}$  /  $\text{MeCN}$  / rt

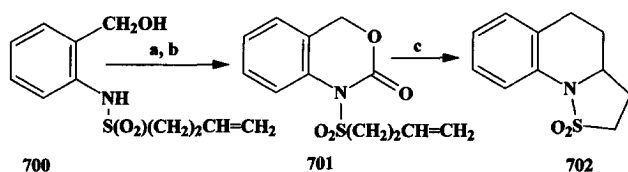
Scheme 118



Scheme 119



Scheme 120



a: BuLi; b: COCl<sub>2</sub>; c: thermolysis/ trifluorobenzene

Scheme 121

## VI. Five Membered Heterocyclo-Quinolines with Three Heteroatoms

### A. TRIAZOLOQUINOLINES

Three classes of triazoloquinolines may exist based on the fusion of the triazole ring on face *a*, *ij* or *j*. This could lead to eight isomeric compounds as shown in Fig. 9.

#### 1. 1,2,3-Triazolol[1,5-*a*]quinolines

Condensation of 2-azido benzonitrile derivatives **703** with ethyl acetonedicarboxylate in presence of NaOEt gave the triazoloquinoline derivatives **705** presumably through the intermediate **704** (90S654). Reaction of **703** with dibenzyl ketone gave the triazole **706** accompanied by **707** which upon treatment with NaH in THF afforded **706** (97S773) (Scheme 122).

The 2-substituted quinoline **708** gave upon reaction with mesitylenesulfonyl hydroxylamine the 1-aminoquinoline salt **709** which could be cyclized with PPA to give **710** (75JHC481). Heating the 2-methylquinoline **711**

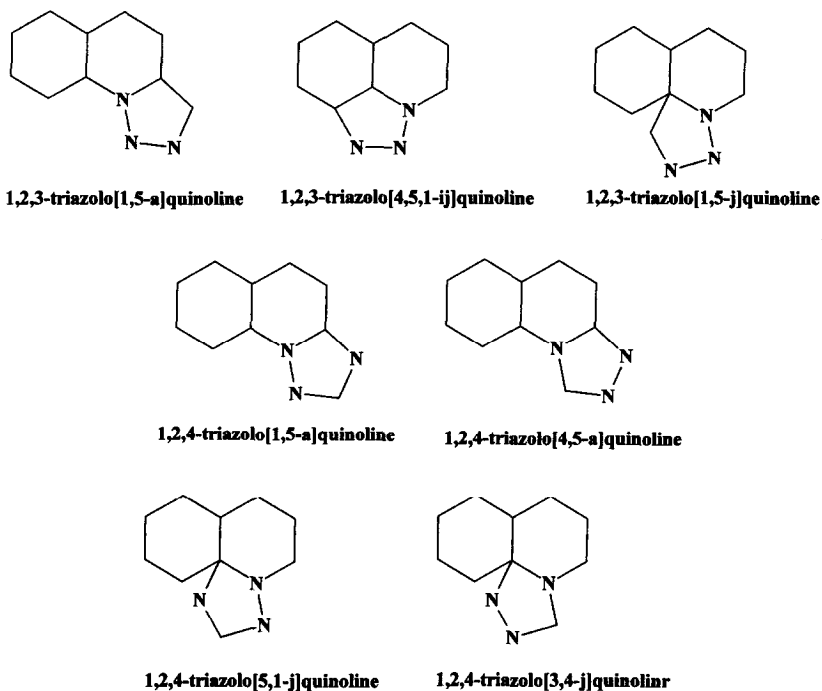
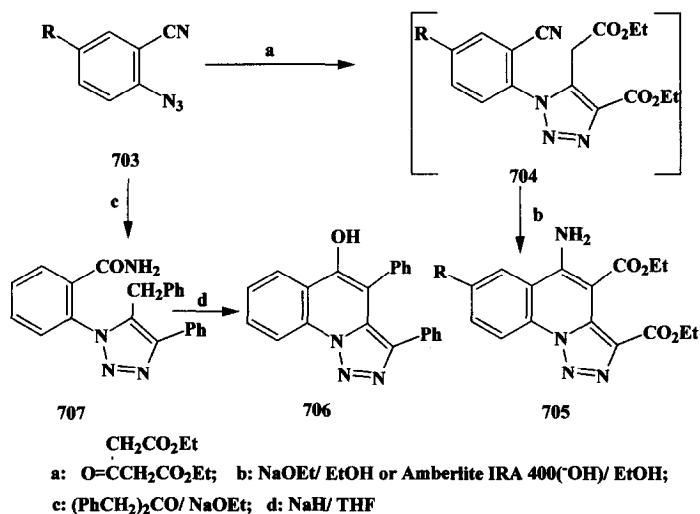
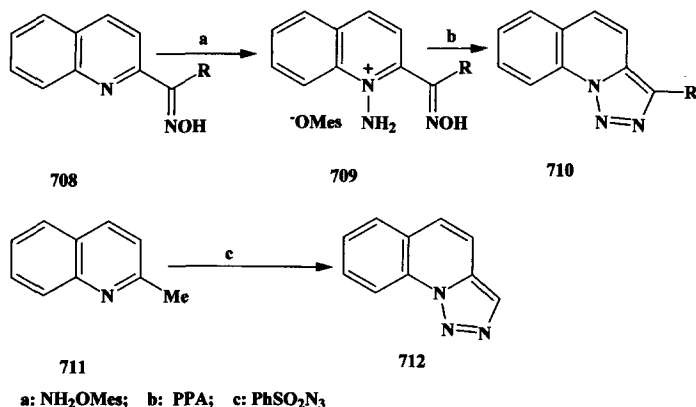


Fig. 9



Scheme 122



Scheme 123

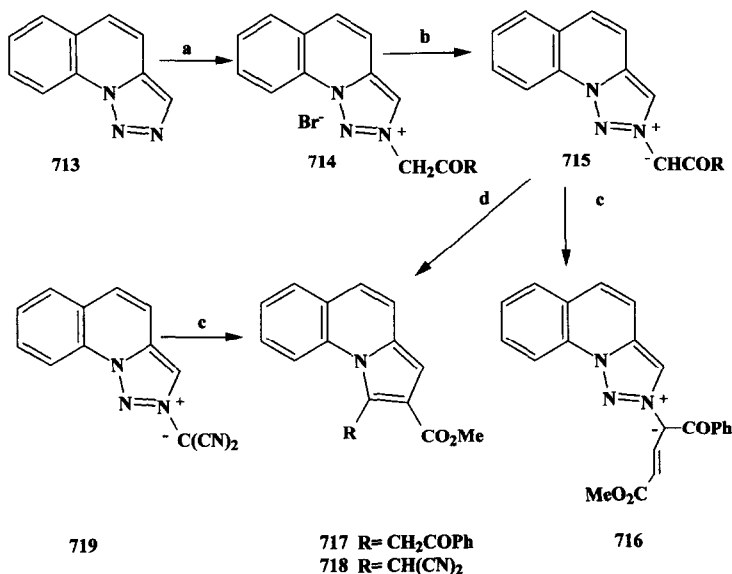
with benzenesulfonyl azide gave the triazoloquinoline **712** presumably via a 2-diazomethylquinoline intermediate (72JOC2025) (Scheme 123).

Quaternization of the triazoloquinoline **713** gave salts that proved to be carrying the quaternary substituent at N-2 a result which is in accord with the *ab initio* calculations (97T12765). Thus, reaction of **713** with  $\alpha$ -bromoacyl compounds in MeCN gave the corresponding quaternary salts **714** which upon treatment with  $\text{K}_2\text{CO}_3$ , afforded the ylides **715**. Treatment of the ylide **715** ( $\text{R} = \text{Ph}$ ) with methyl propiolate in MeCN gave **716** whereas when toluene was used as a solvent instead of MeCN the pyrroloquinoline **717** was obtained. On the other hand, the ylide **719** which upon reaction with methyl propiolate in MeCN afforded **718** (97T12765) (Scheme 124).

Hydrolysis of the amide **720** gave the acid **721**. Boiling **721** in acetic acid for a prolonged period gave the dihydrofuro[3,4-*b*]quinoline **722** whose possible mechanism of formation is shown in Scheme 125 (85JCS(P1)1897).

## 2. 1,2,3-Triazolo[4,5,1-*ij*]quinolines

Intramolecular dipolar azide-olefin cycloaddition of **723** took place upon heating in benzene to afford **724** (83JA3273). An alternative rearrangement process can take place upon photolysis of **724** to give **725**. Mesylation of 4-(3-hydroxypropyl)-2,4,6-trimethyl-2,5-cyclohexadiene-1-one (78JA4618) and subsequent treatment with sodium azide in DMF afforded the respective azide **726** which underwent intramolecular cycloaddition to afford the triazoline **727** (83JOC2432). Irradiation of **727** gave the triazole derivative **728** (Scheme 126).



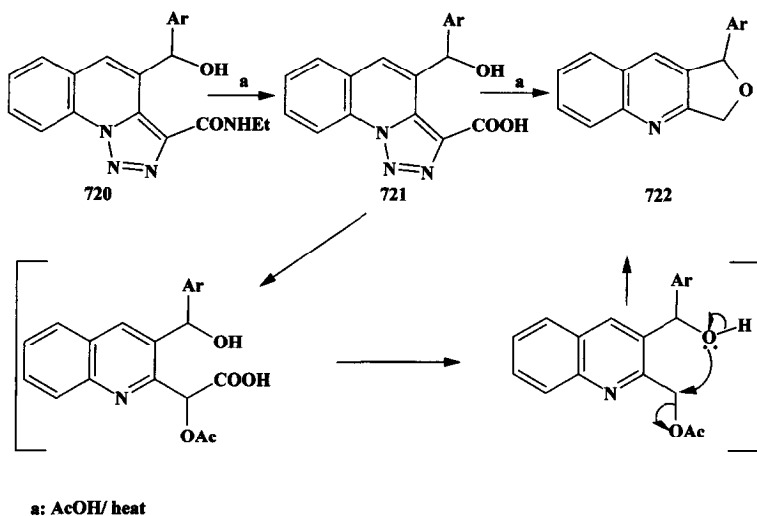
a: BrCH<sub>2</sub>COR(R= OMe, Ph)/ MeCN/ 3 days; b: K<sub>2</sub>CO<sub>3</sub>/ MeCN;

c: HC≡CCO<sub>2</sub>Me/MeCN; d: HC≡CCO<sub>2</sub>Me/ PhMe

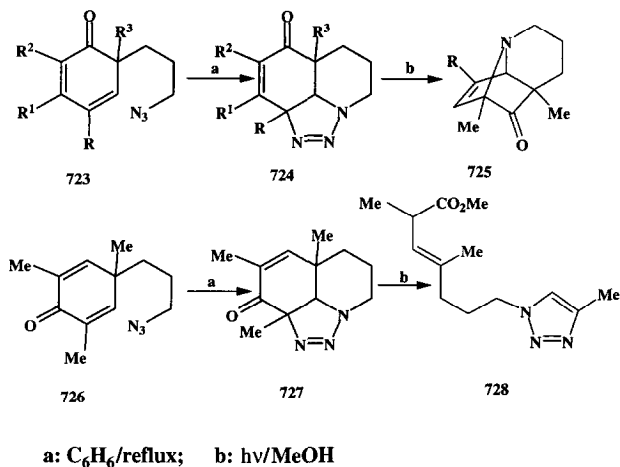
Scheme 124

### 3. 1,2,4-Triazolo[4,5-a]quinolines

The most popular derivatives of quinoline which have been used extensively for the synthesis of this ring system are 2-hydrazinoquinoline and its derivatives. Such compounds were readily prepared by the reaction of hydrazine hydrate with 2-chloroquinolines **729** to give **730**. Various cyclizations of these hydrazines **730** constitutes a source for the annulation of the triazole ring to the quinoline one. Thus, reaction of **730** with aldehydes gave the corresponding hydrazones **731** which upon oxidation gave the respective triazoloquinolines **732** (97CH609), that can also be effected by the fusion (91AP249). Cyclization of **730** with acids or acid chlorides gave **732** via the probable formation of the respective hydrazide **733** that can be readily cyclized by acids or by the action of phosphorus oxychloride to give **732** (91KG493, 90M1017, 97KFZ33). Derivatives of these triazoles were tested for anti-inflammatory activity (91KFZ24, 96KFZ52). Cyclization of 2-hydrazinoquinoline with urea gave **737** (91KG493). Alternatively, reaction of 2-chloroquinoline with semicarbazide hydrochloride gave **734** whose subsequent cyclization with acid gave **737**.



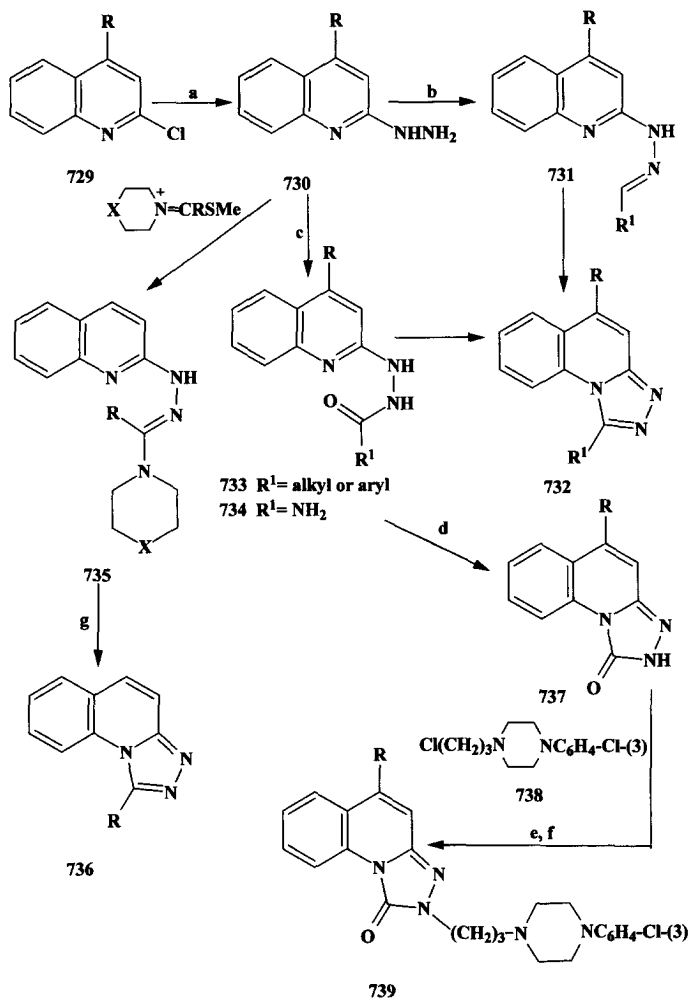
Scheme 125



Scheme 126

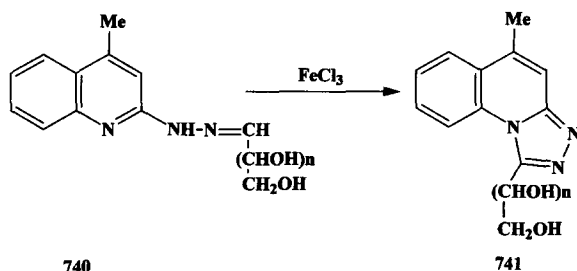
Alkylation of **737** with **738** gave **739** (81USP4252806). Reaction of 2-hydrazinoquinoline with the quaternary salts of N,N-substituted thioamides gave the hydrazones **735** whose cyclization in acetic acid gave triazoloquinolines **736** (80PJC661) (Scheme 127).

The cyclization of the 2-hydrazino-4-methylquinoline derivatives of sugars **740** by the action of ferric chloride to give the acyclic nucleosides **741** (94MI295) (Scheme 128).



Scheme 127

Reaction of **730** with carbon disulfide in pyridine gave the triazoloquinolines **742** (88EP254623, 91AP249, 91KG493, 93MI163). Alkylation of **742** with **743** gave the piperazine **744** (88EP254623). Reaction of **742** with methyl acrylate gave **745** that upon reaction with hydrazine gave the corresponding hydrazide **748** which can be cyclized to the oxadiazole



Scheme 128

derivative **749** (89IJC(B)170). Hydroxymethylation of **742** gave **746** (91AP249) whose subsequent reaction with  $\text{SOCl}_2$  and amines gave **747**. Derivatives of **747** were tested against *S. aureus*, *E. coli* and *Candida albicans* (91AP249) (Scheme 129).

The 2,3-dihydro-1,2,4-triazolo[4,3-*a*]quinolines **751** were prepared by the reaction of 2-ethylhydrazinoquinoline derivatives **750** with aromatic aldehydes (97CH609) (Scheme 130).

Cycloaddition of **752** with tetrazine **753** via [4+2] process followed by N-2 elimination and aromatization afforded **754** (93AP427). Reaction of *N*-arylbenzhydrazonoylchloride **756** with triethylamine gave the nitrilimine **755** which upon reaction with quinoline **752** afforded **757** (92LA885). Electrolysis of a mixture of quinoline **752** and **758** gave triazoloquinolinium perchlorate **759** (85ZC443) (Scheme 131).

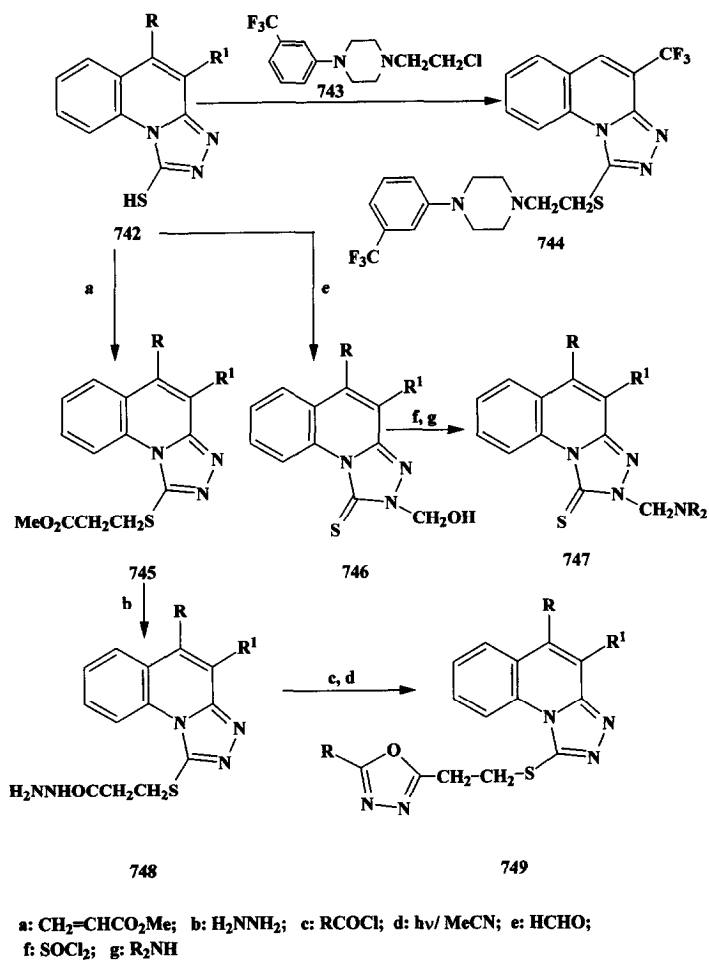
Photocyclization of bromophenyltriazoloquinoline **760** in MeCN gave **761** (89SC2345) (Scheme 132).

Reaction of triazoloquinoline **762** with diethyl ethoxymethylenemalonate gave **763** which upon cyclization gave 10-carbethoxy-9-oxo-9-*H*-pyrimido[1',2':1,5][1,2,4]triazolo[4,3-*a*]quinoline **764**. Treatment of **762** with ethyl acetoacetate or ethyl trifluoroacetoacetate afforded **767** that upon cyclization gave **768**. Reaction of **762** with 2-chloropyridine-3-carboxylic acid chloride or 2-chlorobenzoylchloride afforded **765** (90JHC981) or quinazolinotriazoloquinoline **766**, respectively (91IJC(B)710) (Scheme 133).

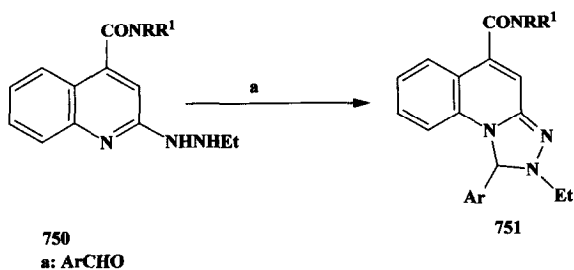
#### 4. 1,2,4-Triazolo[1,5-*a*]quinolines

Reaction of 1-amino-2-cyanoquinolinium perchlorate **769** with triethyl orthoformate gave the formamidine derivative **770** which upon treatment with primary amines afforded the triazoloquinolinium perchlorate **771** (90H289) (Scheme 134).

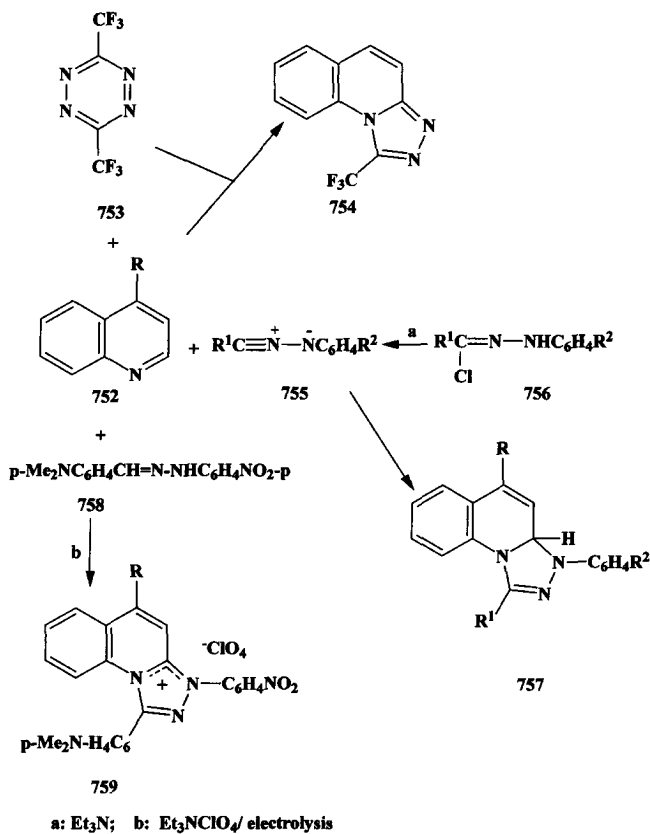




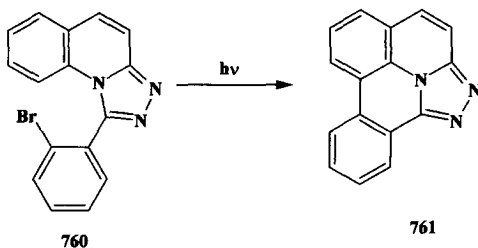
Scheme 129



Scheme 130



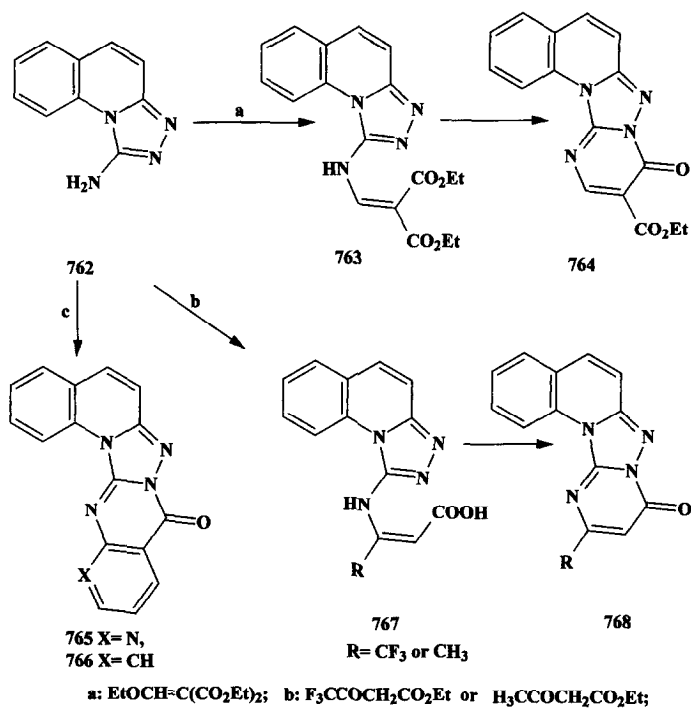
Scheme 131



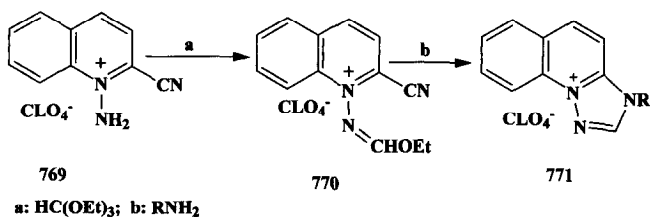
Scheme 132

Rearrangement of oxadiazole bearing quinoline **772** gave the triazoloquinoliny ketoxime **773** (93H1577) (Scheme 135).

Cyclization of the hydrazonyl chloride **774** with triethylamine in refluxing benzene gave a mixture of triazoloquinoline **775** as a minor product

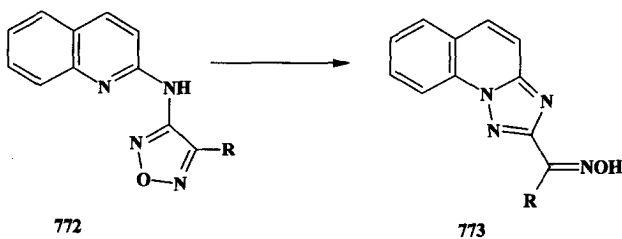


Scheme 133

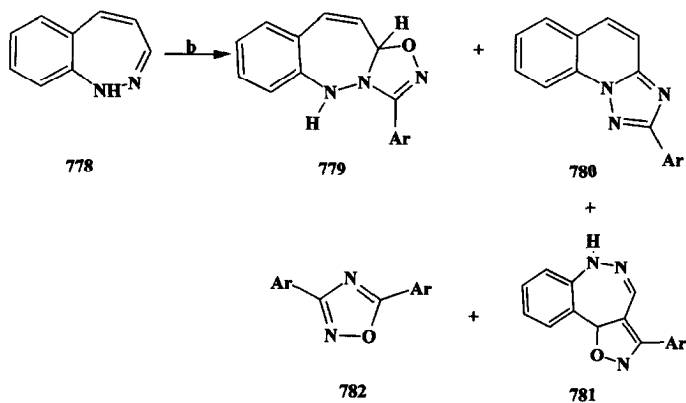
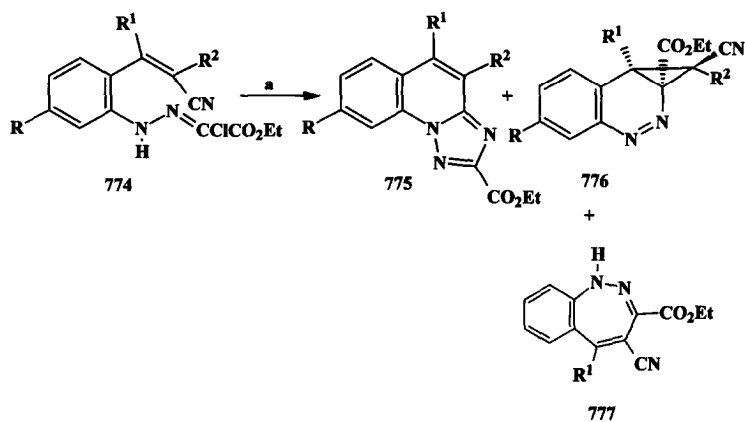


Scheme 134

and cyclopropacinnoline **776** and benzodiazepine **777** (83JCS(P1)539). Similarly, cycloaddition of 3,5-dichloro-2,4,6-trimethylbenzenenitrileoxide and 1,2-benzodiazepine **778** gave the triazoloquinoline **780** as a byproduct together with **779**, **781** and a dimerization product **782** (96H2179) (Scheme 136).



Scheme 135



Scheme 136

## B. THIADIAZOLOQUINOLINES

There are nine possible isomeric compounds for the thiadiazoloquinoline based on the fusion of the thiadiazole ring on the faces *a*, *ij* and *j* and arrangement of the heteroatoms as shown in Fig. 10, from which only one, to the best of our knowledge, was reported: *1,2,4-Thiadiazolo[4,5-a]quinolines*.

### 1. *1,2,4-Thiadiazolo[4,5-a]quinolines*

Reaction of thioacetamide with benzaldehyde in ethanol, NaOH gave **783** that upon electrochemical oxidation afforded acrylonitrile derivative **785** together with the thiadiazoloquinoline derivative **784** (82MI199) (Scheme 137).

## C. ANTIMONYLOXAZOLOQUINOLINES

### 1. *2,1,3-Antimonyloxazol[5,4,3-ij]quinolines*

This ring system was prepared by treatment of quinoline derivative **786** with antimonyl chloride to give **787**. Quinoline derivative **786** was prepared by Mannich reaction on 2,8-dihydroxylepidine with diethylamine and formaldehyde to afford the respective diethylaminomethyl derivative that followed by subsequent nitration. The schistosomicidal activity of **787** was studied (80MI66) (Scheme 138).

## VII. Five Membered Heterocyclo-Quinolines with Four Heteroatoms

### A. TETRAZOLOQUINOLINES

The only known example under such heading is that incorporating four nitrogen atoms, the tetrazoloquinoline. Although they can exist in two annulated ring systems, only examples of one of them, *1,2,3,4-tetrazolo[1,5-a]quinolines* are reported (Fig. 11).

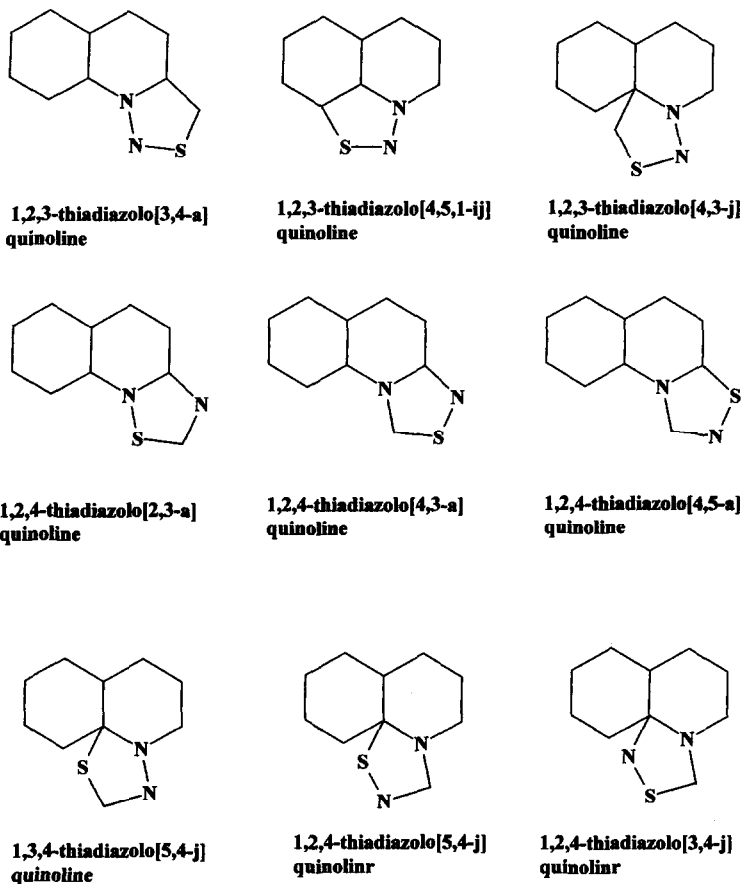
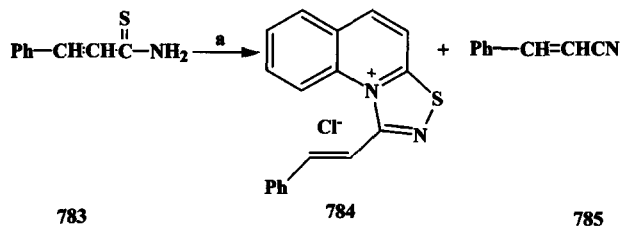
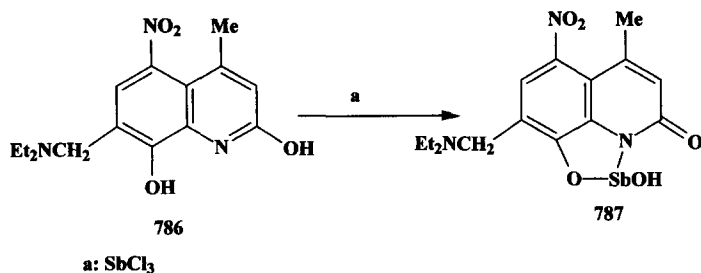


Fig. 10



a: electrochemical oxidation

Scheme 137



Scheme 138

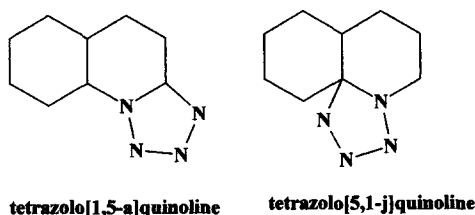


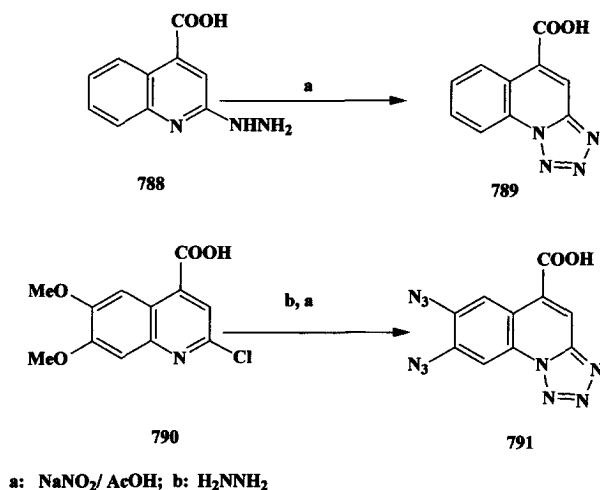
Fig. 11

### 1. 1,2,3,4-Tetrazolo[1,5-a]quinolines

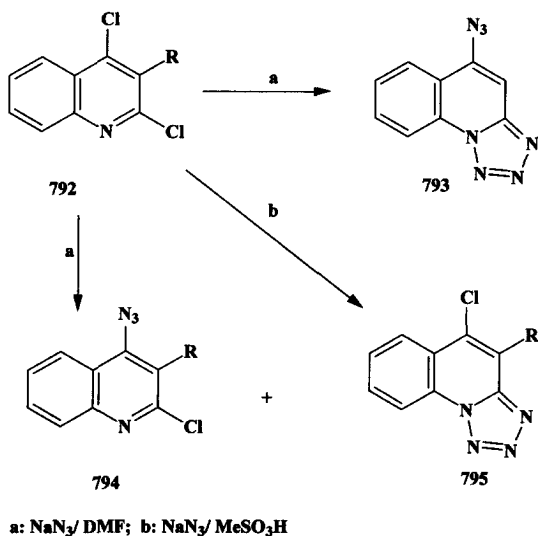
The tetrazoloquinoline such as **789** are readily prepared by reaction of 2-hydrazinocinconic acid **788** with nitrous acid (91KG1227). Reaction of **790** with hydrazine introduces hydrazine residues at positions 2, 6 and 7 whose reaction with nitrous acid gave **791** (90M1017) (Scheme 139).

Reaction of dichloroquinoline **792** with  $\text{NaN}_3$  in DMF gave regioselectively 4-azido-2-chloroquinoline whereas the use of excess azide gave tetrazoloquinoline **793**. Reaction of **792** in which an electron donating group on position 3 with  $\text{NaN}_3$  in DMF afforded a mixture of **794** and **795**. When the reaction was carried out in ethanol with addition of methane sulfonic acid gave regioselectively **795** (94MI311). A number of 4-substituted tetrazoloquinolines were evaluated for antileishmanial and contragestational activities (89IJC(B)562) (Scheme 140).

Base catalyzed condensation of 2-azidobenzaldehyde **796** with cyano-carbanions in piperidine or  $\text{NaOEt}$  in ethanol afforded tetrazoloquinolines **798**  $\text{R} = \text{R}^1 = \text{H}$  (97S773). Thermal cyclization of *o*-azidocinnamionitriles **799** gave **798** (80JOC4767) Reaction of **797** with  $\text{NCCH}_2\text{COR}$  gave **800**



Scheme 139

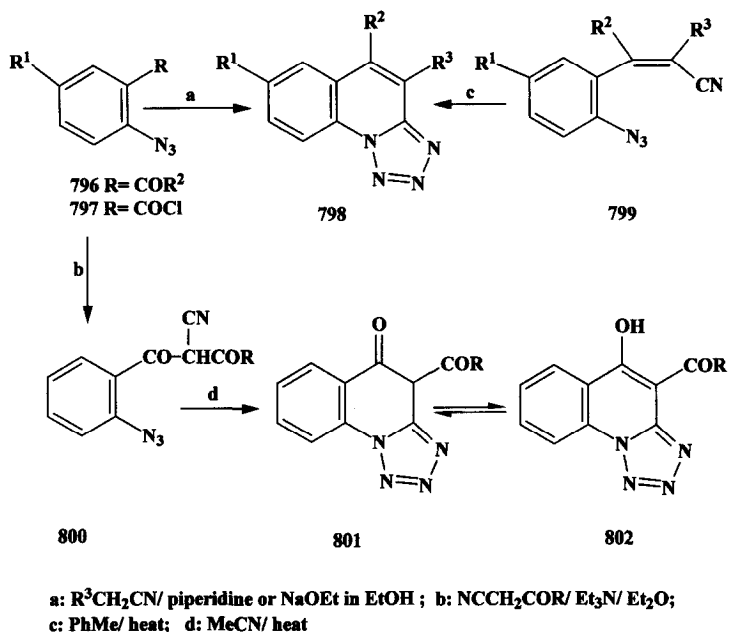


Scheme 140

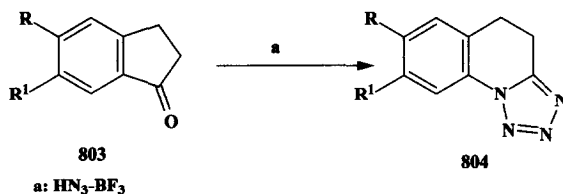
which cyclized upon heating to give **801** that present in the oxy, hydroxy forms **801** and **802** (97S773) (Scheme 141).

Schmidt reaction of indanones **803** by treatment with  $\text{HN}_3\text{-BF}_3$  etherate gave 4,5-dihydro[5,1-*a*]tetrazoloquinoline **804** (92IJC(B)610)) (Scheme 142).





Scheme 141



Scheme 142

## VIII. Conclusions

This chapter includes the recent various aspects of four and five membered heterocyclo-quinolines containing one nitrogen atom at the ring junction. They were subdivided according to the number of heteroatoms in the heterocyclic rings. The literature indicates that many of these heterocycles are of potential therapeutic value which leads to intensive research in the topic. On the other hand, there are various classes of heterocycles that fit under this heading but unreported yet. Consequently, efforts towards the synthesis of such unreported classes can be fruitful area of research.

## REFERENCES

- 63JA2872 G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.* **85**, 2872 (1963).  
65TL2261 Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Lett.*, 2261 (1965).  
67JOC4157 I. J. Borowitz and G. J. Williams, *J. Org. Chem.* **32**, 4157 (1967).  
71BCJ520 Y. Otsuji, K. Yutani, and E. Imoto, *Bull. Chem. Soc. Jpn.* **44**, 520 (1971).  
71CPB832 T. Kato, T. NiiTsuma, and K. Maeda, *Chem. Pharm. Bull.* **19**, 832 (1971).  
72JOC2025 R. A. Abramovitch and T. Takaya, *J. Org. Chem.* **37**, 2025 (1972).  
73T2359 Y. Tamura, S. Matsugashita, H. Ishibashi, and M. Ikeda, *Tetrahedron* **29**, 2359 (1973).  
75JHC119 Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 119 (1975).  
75JHC481 Y. Tamura, J.-H. Kim, Y. Miki, H. Hayashi, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 481 (1975).  
76JMC1111 F. I. Carroll, J. T. Blackwell, A. Philip, and C. E. Twine, *J. Med. Chem.* **19**, 1111 (1976).  
77CPB203 T. Kato, T. Chiba, and H. Kimura, *Chem. Pharm. Bull.* **25**, 203 (1977) [CA **87**, 23,005 (1977)].  
77JCS(P1)2018 B. C. Uff, R. S. Budhram, M. F. Consterdine, J. K. Hicks, B. P. Slingsby, and J. A. Pemblington, *J. Chem. Soc., Perkin Trans. I*, 2018 (1977).  
77LA506 R. Huisgen, R. Grashey, and R. Krischke, *Justus Liebigs Ann. Chem.* 506 (1977) [CA **87**, 39,249 (1977)].  
77MI104 P. V. Borodin, *Khim. Khim. Tekhnol. (Minsk)* **12**, 104 (1977) [CA **88**, 74,287 (1978)].  
77MI471 P. Geneste, J. M. Kamenka, Y. Vidal, M. Besancon, S. Garcet, P. Muller, and C. Warolin, *Eur. J. Med. Chem.-Chim. Ther.* **12**, 471 (1977) [CA **88**, 37,697 (1978)].  
77T1641 G. Lawton, J. E. Saxton, and A. J. Smith, *Tetrahedron* **33**, 1641 (1977).  
77USP4015005 G. E. Hardtmann, U.S. Pat. 4,015,005 (1977) [CA **87**, 39,306 (1977)].  
78BEP858605 S. B. Kadin, Belg. Pat. 858,605 (1978) [CA **89**, 197,540 (1978)].  
78GEP2802493 I. R. Ager and J. P. Ramm, Ger. Offen. 2,802,493 (1978) [CA **89**, 180,001 (1978)].  
78JA4618 E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, and S. Yoo, *J. Am. Chem. Soc.* **100**, 4618 (1978).  
78JAPK7882799 T. Irikura, Jpn. Kokai Tokkyo Koho 78 82,799 (1978) [CA **90**, 22,843 (1979)].  
78JOC2700 K. T. Potts and D. R. Choudhury, *J. Org. Chem.* **43**, 2700 (1978).  
78KG200 R. Fusco and F. Sanniccolo, *Khim. Geterotsikl. Soedin.* 200 (1978) [CA **89**, 6156 (1978)].  
78MI77 H.-S. Kuo, Y.-T. Ma, and Y.-C. Tung, *Hua Hsueh* **77** (1978) [CA **92**, 94,216 (1980)].  
78PJC107 L. Lompa-Krzynien and L. C. Leitch, *Pol. J. Chem.* **52**, 107 (1978) [CA **89**, 43,043 (1978)].  
78TL1887 E. Tighineanu, F. Chiraleu, and D. Raileanu, *Tetrahedron Lett.*, 1978 (1987).

Refs.]	FUSED HETEROCYCLO-QUINOLINES	179
79AP801	R. Neidlein and H. Heid, <i>Arch. Pharm.</i> <b>312</b> , 801 (1979) [ <i>CA</i> <b>92</b> , 76,256 (1980)].	
79BEP872311	P. E. Aldrich and G. H. Berezin, Belg. Pat. 872,311 (1979) [ <i>CA</i> <b>91</b> , 175,218 (1979)].	
79CPB1004	H. Yamanaka, H. Egawa, and T. Sakamoto, <i>Chem. Pharm. Bull.</i> <b>27</b> , 1004 (1979) [ <i>CA</i> <b>91</b> , 56,911 (1979)].	
79H1021	K. Yakushijin, T. Tsuruta, and H. Furukawa, <i>Heterocycles</i> <b>12</b> , 1021 (1979) [ <i>CA</i> <b>91</b> , 211,224 (1979)].	
79JCS(P1)1013	S. Cerrini, W. Fedeli, F. Mazza, G. Lucente, M. P. Paradisi, and A. Romeo, <i>J. Chem. Soc., Perkin Trans. I</i> , 1013 (1979).	
79JCS(P1)3053	P. G. Sammes and A. C. Weedon, <i>J. Chem. Soc., Perkin Trans. I</i> , 3053 (1979).	
79JHC393	H.-S. Kuo, S. Yoshina, and Y.-C. Tung, <i>J. Heterocycl. Chem.</i> <b>16</b> , 393 (1979).	
79JHC689	M. Iwao and T. Kuraishi, <i>J. Heterocycl. Chem.</i> <b>16</b> , 689 (1979).	
79JHC949	V. Shankarnarayan and J. R. Merchant, <i>J. Heterocycl. Chem.</i> <b>16</b> , 949 (1979).	
79JHC1589	G. P. Zecchini and M. P. Paradisi, <i>J. Heterocycl. Chem.</i> <b>16</b> , 1589 (1979).	
79JOC285	C. N. Filer, F. E. Granchelli, P. Perri, and J. L. Neumeyer, <i>J. Org. Chem.</i> <b>44</b> , 285 (1979).	
79KG989	L. T. Gorb, N. N. Romanov, and A. I. Tolmachev, <i>Khim. Geterotsikl. Soedin.</i> 989 (1979) [ <i>CA</i> <b>91</b> , 211,314 (1979)].	
79MI585	J. R. Merchant and V. Shankarnarayan, <i>Curr. Sci.</i> <b>48</b> , 585 (1979) [ <i>CA</i> <b>91</b> , 140,696 (1979)].	
79TL1765	Y. Yamashita and M. Masumura, <i>Tetrahedron Lett.</i> , 2765 (1979).	
79USP4151282	W. J. Welstead Jr. and W. N. Dannenburg, U.S. Pat. 4,151,282 (1979) [ <i>CA</i> <b>91</b> , 134,255 (1979)].	
79YZ813	S. Fukushima, K. Morinaga, S. Sato, H. Kobayashi, and K. Noro, <i>Yakugaku Zasshi</i> <b>99</b> , 813 (1979) [ <i>CA</i> <b>92</b> , 41,885 (1980)].	
80ACSA(B)79	E. K. Pohjala, <i>Acta Chem. Scand., Ser. B</i> <b>B34</b> , 79 (1980) [ <i>CA</i> <b>93</b> , 204,428 (1980)].	
80JA3294	S. F. Martin, S. R. Desai, G. W. Philips, and A. C. Miller, <i>J. Am. Chem. Soc.</i> <b>102</b> , 3294 (1980).	
80JA7154	R. Fujimoto, Y. Kishi, and J. F. Blount, <i>J. Am. Chem. Soc.</i> <b>102</b> , 7145 (1980).	
80JOC4767	L. Garanti and G. Zecchi, <i>J. Org. Chem.</i> <b>45</b> , 4767 (1980).	
80JOMC9	P. Cazeau, F. Moulines, D. Laporte, and F. Dubaudin, <i>J. Organomet. Chem.</i> <b>201</b> , C9 (1980).	
80KG621	L. T. Gorb, A. D. Kachkovskii, N. N. Romanov, I. S. Shpileva, and A. I. Tolmachev, <i>Khim. Geterotsikl. Soedin.</i> 621 (1980) [ <i>CA</i> <b>93</b> , 132,416 (1980)].	
80MI66	H. A. Shoeb, M. I. Korkor, G. H. Tammam, and S. M. El-Amin, <i>Can. J. Pharm. Sci.</i> <b>15</b> , 66 (1980) [ <i>CA</i> <b>94</b> , 192,088 (1981)].	
80N193	G. G. Habermehl and O. Thureau, <i>Naturwissenschaften</i> <b>67</b> , 193 (1980) [ <i>CA</i> <b>93</b> , 132,666 (1980)].	
80PJC661	M. Santus, <i>Pol. J. Chem.</i> <b>54</b> , 661 (1980) [ <i>CA</i> <b>94</b> , 65,565 (1981)].	
80T1385	E. Tighineanu, F. Chiraleu, and D. Raileanu, <i>Tetrahedron</i> <b>36</b> , 1385 (1980).	
81H713	K. J. Baird, M. F. Grundon, D. M. Harrison, and M. G. Magee, <i>Heterocycles</i> <b>15</b> , 713 (1981) [ <i>CA</i> <b>94</b> , 192,047 (1981)].	

- 81JHC1273 F. Babudri, L. D. Nunno, and S. Florio, *J. Heterocycl. Chem.* **18**, 1273 (1981).
- 81KG481 L. T. Gorb, N. N. Romanov, K. V. Fedotov, and A. I. Tolmachev, *Khim. Geterotsikl. Soedin.* 481 (1981) [*CA* **95**, 82,382 (1981)].
- 81LA1751 H. Gnichtel and B. Moeller, *Liebigs Ann. Chem.* 1751 (1981) [*CA* **96**, 20,023 (1982)].
- 81SUP854930 G. G. Skvortsova, D. G. Kim, and L. M. Kim, U.S.S.R. SU Pat. 854,930 (1981) [*CA* **96**, 35,234 (1982)].
- 81T4041 L. E. Overman, M. Sworin, L. S. Bass, and J. Clardy, *Tetrahedron* **37**, 4041 (1981).
- 81TL4197 R. Fujimoto and Y. Kishi, *Tetrahedron Lett.* **22**, 4197 (1981).
- 81USP4252806 D. F. Morrow, U.S. Pat. 4,252,806 (1981) [*CA* **95**, 7294 (1981)].
- 82AP901 R. Neidlein and U. Rietdorf, *Arch. Pharm.* **315**, 901 (1982) [*CA* **98**, 34,479 (1983)].
- 82CPB140 K. Yakushijin, T. Tsuruta, and H. Furukawa, *Chem. Pharm. Bull.* **30**, 140 (1982) [*CA* **96**, 181,117 (1982)].
- 82EP58392 S. Matsumura, M. Kise, M. Ozaki, S. Tada, K. Kazuno, H. Watanabe, K. Kunitomo, M. Tsuda, H. Enomoto et al., Eur. Pat. EP 58,392 (1982) [*CA* **98**, 53,877 (1983)].
- 82EP62580 A. C. Barnes and P. A. Robson, Eur. Pat. EP 62,580 (1982) [*CA* **98**, 53,901 (1983)].
- 82JAPK8202285 Otsuka Pharmaceutical Co. Ltd. Jpn. Kokai Tokkyo Koho JP 82 02,285 (1982) [*CA* **96**, 217,717 (1982)].
- 82JAPK57203085 Daiichi Seiyaku Co. Ltd. Jpn. Kokai Tokkyo Koho JP 57 203,085 (1982) [*CA* **98**, 198,294 (1983)].
- 82JCS(P1)1593 R. E. Banks and S. M. Hitchen, *J. Chem. Soc., Perkin Trans. I*, 1593 (1982).
- 82JHC573 R. J. Sundberg and J. E. Ellis, *J. Heterocycl. Chem.* **19**, 573 (1982).
- 82JHC837 W. S. Saari, W. Halczenko, M. B. Freedman, and B. H. Arison, *J. Heterocycl. Chem.* **19**, 837 (1982).
- 82JOC688 M. Cardellini, G. M. Cingolani, F. Claudi, G. Cristalli, U. Gulini, and S. Martelli, *J. Org. Chem.* **47**, 688 (1982).
- 82M623 R. Neidlein and U. Rietdorf, *Montash. Chem.* **113**, 623 (1982) [*CA* **97**, 109,848 (1982)].
- 82MI199 T. Karakasa and M. Sato, *Nippon Shika Daigaku Kiyo, Ippan Kyoiku-Kei* **11**, 199 (1982) [*CA* **97**, 127,575 (1982)].
- 82S1088 C. Deshayes, M. Chabannet, and S. Gelin, *Synthesis*, 1088 (1982).
- 82TL919 U. C. Yoon, S. L. Quillen, P. S. Mariano, R. Swanson, J. L. Stavinoha, and E. Bay, *Tetrahedron Lett.* **23**, 919 (1982).
- 82TL4501 R. D. Bowen, D. E. Davies, C. W. G. Fishwick, T. O. Glasbey, S. J. Noyce, and R. C. Storr, *Tetrahedron Lett.* **23**, 4501 (1982).
- 83EP90516 J. F. Egger, M. R. Johnson, and L. S. Melvin, Eur. Pat. EP 90,516 (1983) [*CA* **100**, 138,970 (1984)].
- 83JA1204 U. C. Yoon, S. L. Quillen, P. S. Mariano, R. Swanson, J. L. Stavinoha, and E. Bay, *J. Am. Chem. Soc.* **105**, 1204 (1983).
- 83JA3273 A. G. Schultz, J. P. Dittami, S. O. Myong, and C.-K. Sha, *J. Am. Chem. Soc.* **105**, 3273 (1983).
- 83JAPK5813585 Otsuka Pharmaceutical Co. Ltd. Jpn. Kokai Tokkyo Koho JP 58 13,585 (1983) [*CA* **98**, 198,053 (1983)].
- 83JCED283 R. S. Tewari, P. D. Dixit, and A. K. Dubey, *J. Chem. Eng. Data* **28**, 283 (1983) [*CA* **98**, 143,253 (1983)].

- 83JCS(CC)431 R. Joyeau, Y. Dugenet, and M. Wakselman, *J. Chem. Soc., Chem. Commun.*, 431 (1983).
- 83JCS(P1)539 L. Bruche, L. Garanti, and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 539 (1983).
- 83JCS(P1)1925 M. D. Bachi and J. Klein, *J. Chem. Soc., Perkin Trans. 1*, 1983 (1925).
- 83JHC139 C. Banzatti, A. D. Torre, P. Melloni, D. Pieraccioli, and P. Salvadori, *J. Heterocycl. Chem.* **20**, 139 (1983).
- 83JOC2432 A. G. Schultz and S. O. Myong, *J. Org. Chem.* **48**, 2432 (1983).
- 83KG1664 V. A. Kaminskii, T. V. Zabolotnova, T. V. Novikova, and M. N. Tilichenko, *Khim. Geterotsikl. Soedin.* 1664 (1983) [*CA* **100**, 191,709 (1984)].
- 84ACSA(B)109 B. A. Johnsen and K. Undheim, *Acta Chem. Scand., Ser. B* **B38**, 109 (1984) [*CA* **101**, 23,306 (1984)].
- 84AP951 F. S. G. Soliman, S. M. Rida, E. S. A. M. Badawy, and T. Kappa, *Arch. Pharm.* **317**, 951 (1984) [*CA* **102**, 24,549 (1985)].
- 84CS38 G. Lindgren, *Chem. Scr.* **24**, 38 (1984) [*CA* **102**, 6307 (1985)].
- 84EP115334 H. Ishikawa, T. Uno, H. Miyamoto, and K. Nakagawa, Eur. Pat. EP 115,334 (1984) [*CA* **102**, 24,507 (1985)].
- 84GBP2127824 W. R. Tully, Brit. UK Pat. GB 2,127,824 (1984) [*CA* **101**, 171,248 (1984)].
- 84H2467 Y. Miki, N. Nishikubo, Y. Nomura, H. Kinoshita, S. Takemura, and M. Ikeda, *Heterocycles* **22**, 2467 (1984) [*CA* **102**, 78,767 (1985)].
- 84JAPK5978189 Otsuka Pharmaceutical Co. Ltd. Jpn. Kokai Tokkyo Koho JP 59 78,189 (1984) [*CA* **101**, 151,767 (1984)].
- 84JAPK59134792 Nippon Kayaku Co. Ltd. Jpn. Kokai Tokkyo Koho JP 59 134,792 (1984) [*CA* **102**, 6222 (1985)].
- 84MI215 G. Winters, G. Odasso, M. Conti, G. Tarzia, and G. Galliani, *Eur. J. Med. Chem.-Chim. Ther.* **19**, 215 (1984) [*CA* **102**, 78,764 (1985)].
- 84MI1078 J. Sakai, K. Ikeda, and Y. Ishida, *Iyakuhiin Kenkyu* **15**, 1078 (1984) [*CA* **102**, 119,508 (1985)].
- 85EP139584 D. M. Bigg, C. M. Morel, and M. Sevrin, Eur. Pat. EP 139,584 (1985) [*CA* **103**, 71,317 (1985)].
- 85EP146369 R. Crossley, Eur. Pat. EP 146,369 (1985) [*CA* **103**, 141,963 (1985)].
- 85EP146370 R. Crossley, Eur. Pat. EP 146,370 (1985) [*CA* **103**, 215,289 (1985)].
- 85JCS(P1)1897 B. Abarca, R. Ballesteros, E. Gomez-Aldaravi, and G. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1985 (1897).
- 85JHC1049 M. Noguchi, N. Tanigawa, and S. Kajigaeshi, *J. Heterocycl. Chem.* **22**, 1049 (1985).
- 85JMC298 N. P. Peet, L. E. Baugh, S. Sunder, and J. E. Lewis, *J. Med. Chem.* **28**, 298 (1985).
- 85JOC722 W. K. Anderson, J. DeRuiter, and A. R. Heider, *J. Org. Chem.* **50**, 722 (1985).
- 85S619 T. Eicher and R. Rohde, *Synthesis*, 619 (1985).
- 85USP4550104 T. F. Mich and J. P. Sanchez, U.S. Pat. 4,550,104 (1985) [*CA* **104**, 168,455 (1986)].
- 85ZC443 W. Jugelt, L. Grubert, and V. Paulss, *Z. Chem.* **25**, 443 (1985) [*CA* **106**, 138,190 (1987)].
- 86CCC412 J. Stetinova, A. Jurasek, J. Kovac, M. Dandarova, and P. Safar, *Collect. Czech. Chem. Commun.* **51**, 412 (1986) [*CA* **105**, 226,262 (1986)].
- 86CPB2435 A. Kakehi, S. Ito, and T. Yotsuya, *Chem. Pharm. Bull.* **34**, 2435 (1986) [*CA* **106**, 196,290 (1987)].

- 86EP172097 P. George and D. De Peretti, Eur. Pat. EP 172,097 (1986) [CA **105**, 97,467 (1986)].
- 86H2109 S. Nakatsuka, O. Asano, and T. Goto, *Heterocycles* **24**, 2109 (1986) [CA **106**, 49,948 (1987)].
- 86IZV2074 A. E. Zelenin, N. D. Chkanikov, A. M. Umnov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.* 2074 (1989) [CA **107**, 134,173 (1987)].
- 86JOC4077 D. F. Taber, R. E. Ruckle, Jr., and M. J. Hennesy, *J. Org. Chem.* **51**, 4077 (1986).
- 86S908 T. Eicher and W. Freihoff, *Synthesis*, 908 (1986).
- 86USP4593092 T. Irikura, K. Takagi, S. Fujimori, and Y. Hirata, U.S. Pat. 4,593,092 (1986) [CA **105**, 114,900 (1986)].
- 87CJC104 G. Just and G. Sacripante, *Can. J. Chem.* **65**, 104 (1987) [CA **108**, 5726 (1988)].
- 87EP231138 P. George and D. De Peretti, EP 231,138 (1987) [CA **109**, 129,002 (1988)].
- 87FRP2593179 P. George and D. De Peretti, Fr. Demande FR 2,593,179 (1987) [CA **109**, 73,430 (1988)].
- 87GBP2190376 M. Kise, M. Kitano, M. Ozaki, K. Kazuno, I. Shirahase, Y. Tomii, and J. Segawa, Brit. UK Pat. GB 2,190,376 (1987) [CA **108**, 94,537 (1988)].
- 87JA3136 W. H. N. Nijhuis, W. Verboom, D. N. Reinhoudt, and S. Harkema, *J. Am. Chem. Soc.* **109**, 3136 (1987).
- 87JAPK6233188 T. Ueda and H. Mivamoto, Jpn. Kokai Tokkyo Koho JP 62 33,188 (1987) [CA **107**, 7219 (1987)].
- 87JCS(CC)524 K. C. Majumdar and S. K. Chattopadhyay, *J. Chem. Soc., Chem. Commun.*, 524 (1987).
- 87JCS(P1)1899 R. Joyeau, L. D. S. Yadav, and M. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1987 (1989).
- 87JHC869 J. Reisch, A. Bathe, B. H. W. Rosenthal, and R. A. Salehi-Artimani, *J. Heterocycl. Chem.* **24**, 869 (1987).
- 87JHC1537 D. T. W. Chu and A. K. Claiborne, *J. Heterocycl. Chem.* **24**, 1538 (1987).
- 87JOC3930 L. W. Deady and D. M. Werden, *J. Org. Chem.* **52**, 3930 (1987).
- 87JOC4423 A. Hosomi, S. Hayashi, K. Hoashi, S. Kohra, and Y. Tominaga, *J. Org. Chem.* **52**, 4423 (1987).
- 87KG690 V. P. Litvinov, Yu. A. Sharanin, E. E. Apenova, A. M. Shestopalov, V. Yu. Mortikov, V. N. Nesterov, V. E. Shklover, and Yu. T. Struchkov, *Khim. Geterotsikl. Soedin.* 690 (1987) [CA **108**, 75,270 (1988)].
- 87SUP1336949 H. Ishikawa, F. Tabusa, K. Nakagawa, U.S.S.R. SU 1,336,949 (1987) [CA **109**, 54,571 (1988)].
- 87SC319 L. W. Deady and D. M. Werden, *Synth. Commun.* **17**, 319 (1987) [CA **107**, 175,857 (1987)].
- 87USP4659734 H. Enomoto, M. Kise, M. Ozaki, M. Kitano, and I. Morita, U.S. Pat. 4,659,734 (1987) [CA **107**, 154,254 (1987)].
- 87USP4675323 P. George and D. De Peretti, U.S. Pat. 4,675,323 (1987) [CA **107**, 198,330 (1987)].
- 88CIL94 D. P. Kay, P. D. Kennewell, and R. Westwood, *Chem. Ind. (London)* 94 (1988) [CA **109**, 128,899 (1988)].

- 88EP254623 N. D. Bru-Magniez, J. M. Teulon, and M. Launay, Eur. Pat. EP 254,623 (1988) [CA 109, 93,071 (1988)].
- 88EP286089 M. Taguchi, H. Kondo, Y. Inoue, Y. Kawahata, and G. Tsukamoto, Eur. Pat. EP 286,089 (1988) [CA 110, 135,248 (1989)].
- 88JHC1567 V. D. Parikh, A. H. Fray, and E. F. Kleinman, *J. Heterocycl. Chem.* **25**, 1567 (1988).
- 88S792 E. B. Choi, I. K. Youn, and C. S. Pak, *Synthesis*, 792 (1988).
- 88UKZ295 Yu. M. Volovenko, A. G. Nemazanyi, I. G. Ryabokon, and F. S. Babichev, *Ukr. Khim. Zh. (Russ. Ed.)* **54**, 295 (1988) [CA 110, 38,921 (1989)].
- 89AKZ636 L. V. Gyulbudagyan, I. L. Aleksanyan, and A. A. Avetisyan, *Arm. Khim. Zh.* **42**, 636 (1989) [CA 113, 40,544 (1990)].
- 89EP315827 M. Kise, M. Kitano, M. Ozaki, K. Kazuno, M. Matsuda, I. Shirahase, and Y. Tomii, Eur. Pat. EP 315,827 (1989) [CA 111, 232,779 (1989)].
- 89EP315828 M. Kise, M. Kitano, M. Ozaki, K. Kazuno, M. Matsuda, I. Shirahase, and J. Segawa, Eur. Pat. EP 315,828 (1989) [CA 111, 194,791 (1989)].
- 89EP322016 D. Hamminga, H. H. Haeck, I. Van Wijngaarden, and W. Wouters, Eur. Pat. EP 322,016 (1989) [CA 112, 55,597 (1990)].
- 89GEP3840097 H. Walter, Ger Offen. DE 3,840,097 (1989) [CA 111, 235,043 (1989)].
- 89IJC(B)170 R. Rama and V. R. Srinivasan, *Indian J. Chem., Sect. B* **28**(B), 170 (1989) [CA 112, 35,760 (1990)].
- 89IJC(B)562 R. P. Srivastava, M. Seth, A. P. Bhaduri, S. Bhatnagar, and P. Y. Guru, *Indian J. Chem., Sect. B* **28**(B), 562 (1989) [CA 112, 138,965 (1990)].
- 89IZV472 K. V. Komarov, N. D. Chkanikov, V. I. Suskina, A. B. Shapiro, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.* 472 (1989) [CA 111, 153,587 (1989)].
- 89JHC1555 C. O. Kappe and T. Kappa, *J. Heterocycl. Chem.* **26**, 1555 (1989).
- 89JOC199 W. H. N. Nijhuis, W. Verboom, A. Abu-El-fadl, S. Harkema, and D. N. Reinhoudt, *J. Org. Chem.* **54**, 199 (1989).
- 89JOC4673 A. I. Meyers and D. Berney, *J. Org. Chem.* **54**, 4673 (1989).
- 89KG1514 N. S. Prostakov, V. V. Kuznetsov, and E. E. Stashenko, *Kim. Getrotsikl. Soedin.* 1514 (1989) [CA 113, 40,424 (1990)].
- 89S322 D. St.C. Black, A. J. Ivory, P. A. Keller, and N. Kumar, *Synthesis*, 322 (1989).
- 89SC2345 M. R. Devi, J. M. Rao, and V. R. Srinivasan, *Synth. Commun.* **19**, 2345 (1989) [CA 112, 198,227 (1990)].
- 89TL6661 W. H. Pearson and Y.-F. Poon, *Tetrahedron Lett.* **30**, 6661 (1989).
- 89WOP8912055 J. Hosomi, Y. Asahina, and S. Suzue, Pct. Int. WO 89 12,055 (1989) [CA 113, 6328 (1990)].
- 90CPB2459 H. Ishikawa, T. Uno, H. Miyamoto, H. Ueda, H. Tamaoka, M. Tominaga, and K. Nakagawa, *Chem. Pharm. Bull.* **38**, 2459 (1990) [CA 114, 101,673 (1991)].
- 90DOK1156 A. M. Shestopalov, V. P. Litvinov, Yu. A. Sharanin, and G. E. Khoroshilov, *Dokl. Akad. Nauk SSSR* **312**, 1156 (1990) [CA 114, 6262 (1991)].
- 90EP375045 D. Hamminga, I. Van Wijngaarden, H. H. Haeck, and W. Wouters, Eur. Pat. EP 375,045 (1990) [CA 114, 6505 (1991)].
- 90EP390135 S. Fujii, H. Ishikawa, H. Tsubouchi, and K. Jitsukawa, Eur. Pat. EP 390,135 (1990) [CA 114, 102,053 (1991)].

- 90EP393538 Y. Itoh, H. Kato, E. Koshinaka, N. Ogawa, N. Yagi, T. Yoshida, and T. Suzuki, Eur. Pat. EP 393,538 (1990) [CA 114, 143,397 (1991)].
- 90EP403980 Y. Kohno and E. Kojima, Eur. Pat. EP 403,980 (1990) [CA 114, 207,056 (1991)].
- 90H289 S. Batori, P. Sandor, and A. Messmer, *Heterocycles* **31**, 289 (1990) [CA 113, 132,092 (1990)].
- 90IZV2627 V. A. Mamedov, I. A. Nuretdinov, and F. G. Sibgatullina, *Izv. Akad. Nauk SSSR, Ser. Chem.* 2627 (1990) [CA 114, 122,182 (1991)].
- 90JAPK02174783 Y. Ito, H. Kato, E. Etsuchu, N. Ogawa, N. Yagi, T. Yoshida, and T. Suzuki, Jpn. Kokai Tokkyo Koho JP 02 174,783 (1990) [CA 113, 231,357 (1990)].
- 90JCS(P1)385 R. C. F. Jones, M. J. Smallridge, and C. B. Chapleo, *J. Chem. Soc., Perkin Trans. 1*, 385 (1990).
- 90JHC263 Y. Tominaga, Y. Ichihara, T. Mori, C. Kamio, and A. Hosomi, *J. Heterocycl. Chem.* **27**, 263 (1990).
- 90JHC981 T. Ramalingam, M. S. R. Murty, Y. V. D. Naheawar, and P. B. Sattur, *J. Heterocycl. Chem.* **27**, 981 (1990).
- 90JHC2151 B. McKittrick, A. Failli, R. J. Steffan, R. M. Soll, P. Hughes, J. Schmid, A. A. Asselin, C. C. Shaw, R. Noureldin, G. Gavin,, *J. Heterocycl. Chem.* **27**, 2151 (1990).
- 90JOC560 M. R. Pavia, W. H. Moos, and F. M. Hershenson, *J. Org. Chem.* **55**, 560 (1990).
- 90KG337 N. V. Shorina, G. A. Golubeva, L. A. Sviridiva, and V. N. Torocheshnikov, *Khim. Geterotsikl. Soedin.* 337 (1990) [CA 113, 131,930 (1990)].
- 90KG388 V. S. Velezheva and S. Yu. Ryabova, *Khim. Geterotsikl. Soedin.* 388 (1990) [CA 113, 115,188 (1990)].
- 90M1017 I. A. Shehata,, *Monatsh. Chem.* **121**, 1017 (1990).
- 90S654 R. K. Smalley and M. Teguiche, *Synthesis*, 654 (1990).
- 91AAC2496 M. Ozaki, M. Matsuda, Y. Tomii, K. Kimura, J. Segawa, M. Kitano, M. Kise, K. Shibata, M. Otsuki, T. Nishino,, *Antimicrob. Agents Chemother.* **35**, 2496 (1991).
- 91AP249 M. A. Khalil, N. S. Habilb, A. M. Farghaly, and O. A. El-Sayed, *Arch. Pharm.* **324**, 249 (1991).
- 91EP405442 H. Inaba, K. Nishijima, K. Kato, I. Yamamoto, E. Mochida, and K. Ohtomo, Eur. Pat. EP 405,442 (1991) [CA 115, 29,328 (1991)].
- 91EP414023 M. Matsuo, T. Manabe, H. Okumura, H. Matsuda, and N. Fujii, Eur. Pat. EP 414,023 (1991) [CA 115, 49,425 (1991)].
- 91H2373 S. Ito, A. Kakehi, and T. Miwa, *Heterocycles* **32**, 2373 (1991) [CA 116, 194,216 (1992)].
- 91IJC(B)710 T. Ramalingam and M. S. R. Murty, *Indian J. Chem., Sect. B* **30(B)**, 710 (1991) [CA 115, 92,214 (1991)].
- 91JAPK0356489 Y. Ito, H. Kato, E. Etsuchu, N. Ogawa, N. Yagi, T. Yoshida, and T. Suzuki, Jpn. Kokai Tokkyo Koho JP 03 56,489 (1991) [CA 115, 49,671 (1991)].
- 91JAPK03109388 Y. Inamoto, S. Kawai, K. Sanada, and T. Endo, Jpn. Kokai Tokkyo Koho JP 03 109,388 (1991) [CA 115, 279,995 (1991)].
- 91JAPK03218383 M. Kise, M. Kitano, M. Ozaki, K. Kazuno, and M. Matsuda, Jpn. Kokai Tokkyo Koho JP 03 218,383 (1991) [CA 116, 41,483 (1992)].



- 91JAPK03261788 Y. Ito, H. Kato, E. Etchu, N. Ogawa, N. Yagi, T. Yoshida, and T. Suzuki, Jpn. Kokai Tokkyo Koho JP 03 261,788 (1991) [CA **116**, 174,132 (1992)].
- 91JHC77 L. Bouyazza, J.-C. Lancelot, S. Rault, and M. Robba, *J. Heterocycl. Chem.* **28**, 77 (1991).
- 91JHC1715 P. Kolar, A. Petric, M. Tisler, and F. Felluga, *J. Heterocycl. Chem.* **28**, 1715 (1991).
- 91JMC168 D. T. W. Chu, C. W. Nordeen, D. J. Hardy, R. N. Swanson, W. J. Giardina, A. G. Pernet, and J. J. Plattner, *J. Med. Chem.* **34**, 168 (1991).
- 91JOC980 A. Chilin, P. Rodighiero, G. Pastorini, and A. Guiotto, *J. Org. Chem.* **56**, 980 (1991).
- 91KFZ24 O. A. Yanborisova, V. E. Kolla, S. A. Vikhareva, and M. E. Kon'shin, *Khim.-Pharm. Zh.* **25**, 24 (1991) [CA **115**, 71,483 (1991)].
- 91KG493 O.Ya. Yanborisova and M. E. Kon'shin, *Khim. Geterotsikl. Soedin.*, 493 (1991).
- 91KG947 V. V. Kuznetsov, A. E. Aliev, A. R. Palma, A. V. Varlamov, and N. S. Prostakov, *Khim. Geterotsikl. Soedin.* 947 (1991) [CA **116**, 106,057 (1992)].
- 91KG1227 O. A. Yanborisova and M. E. Kon'shin, *Khim. Geterotsikl. Soedin.*, 1227 (1991).
- 91MI104 D. G. Kim and N. P. Brisnyuk, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **34**, 104 (1991) [CA **116**, 151,526 (1992)].
- 91MI120 D. G. Kim, N. P. Brisnyuk, and E. A. Lykasova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **34**, 120 (1991) [CA **116**, 106,141 (1992)].
- 91MI251 Y. Hu, K. Lin, Y. Wu, H. Zhou, and R. Fang, *Zhejiang Yike Daxue Xuebao* **20**, 251 (1991) [CA **117**, 90,206 (1992)].
- 91RTC115 E. Kelderman, H. G. Noorlander-Bunt, J. Van Eerden, W. Verboom, and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **110**, 115 (1991) [CA **115**, 183,041 (1991)].
- 91WOP9107412 M. Kise, M. Kitano, M. Ozaki, Y. Tomii, and J. Segawa, *Pct. Int. WO* 91 07,412 (1991) [CA **115**, 114,547 (1991)].
- 91ZN(B)1110 P. Kolar and M. Tisler, *Z. Naturforsch., B: Chem. Sci.* **46**, 1110 (1991) [CA **115**, 232,135 (1991)].
- 92EP465716 Y. Ito, H. Kato, E. Koshinaka, N. Ogawa, N. Yagi, T. Yoshida, and T. Suzuki, *Eur. Pat. EP* 465,716 (1992) [CA **116**, 235,615 (1992)].
- 92IJC(B)610 S. Sudan, R. Gupta, P. L. Kachroo, D. K. Gupta, and K. K. Bhutani, *Indian J. Chem., Sect. B* **31(B)**, 610 (1992).
- 92JAPK04139126 H. Ishikawa, H. Tsuboshi, and K. Jitsukawa, Jpn. Kokai Tokkyo Koho JP 04 139,126 (1992) [CA **117**, 251,242 (1992)].
- 92JAPK04178326 Y. Ito, H. Kato, and T. Sasaki, Jpn. Kokai Tokkyo Koho JP 04 178,326 (1992) [CA **117**, 226,309 (1992)].
- 92JAPK04253982 Y. Ito, H. Kato, S. Yasuda, T. Yoshida, and Y. Yamamoto, Jpn. Kokai Tokkyo Koho JP 04 253,982 (1992) [CA **118**, 101,930 (1993)].
- 92JAPK04356491 Y. Ito, H. Kato, S. Yasuda, T. Yoshida, and Y. Yamamoto, Jpn. Kokai Tokkyo Koho JP 04 356,491 (1992) [CA **119**, 95,504 (1993)].
- 92JCRS260 H. Z. Alkhatlan, *J. Chem. Res., Synop.* 260 (1992) [CA **117**, 171,185 (1992)].
- 92JHC1117 J. Segawa, M. Kitano, K. Kazuno, M. Tsuda, I. Shirahase, M. Ozaki, M. Matsuda, and M. Kise, *J. Heterocycl. Chem.* **29**, 1117 (1992).

- 92JLCR933 M. W. Moon and R. S. P. Hsi, *J. Labelled Compd. Radiopharm.* **31**, 933 (1992) [*CA* **118**, 101,872 (1993)].
- 92JMC1076 M. W. Moon, J. K. Morris, R. F. Heier, C. G. Chidester, W. E. Hoffmann, M. F. Pietcey, J. S. Althaus, P. F. Von Voigtlander, D. L. Evans, L. M. Figur, R. A. Lahti., *J. Med. Chem.* **35**, 1076 (1992).
- 92JMC4727 J. Segawa, M. Kitano, K. Kazuno, M. Matsuoka, I. Shirahase, M. Ozaki, M. Matsuda, Y. Tomii, and M. Kise, *J. Med. Chem.* **35**, 4727 (1992).
- 92JOC4206 E. G. Occhiato, A. Guarna, A. Brandi, A. Got, and F. De Sarlo, *J. Org. Chem.* **57**, 4206 (1992).
- 92JOC4404 A. G. H. Wee, B. Liu, and L. Zhang, *J. Org. Chem.* **57**, 4404 (1992).
- 92JOC5666 A. Brandi, Y. Durust, F. M. Cordero, and F. De Sarlo, *J. Org. Chem.* **57**, 5666 (1992).
- 92JOC6991 B. J. Newhouse, J. Bordner, D. J. Augeri, C. S. Litts, and E. F. Kleinman, *J. Org. Chem.* **57**, 6991 (1992).
- 92LA885 L. Grubert, W. Jugelt, H. J. BreB, H. Koppel, U. Striezel, and A. Dombrowski, *Liebigs Ann. Chem.*, 885 (1992).
- 92MI57 Y. Asahina, T. Ishizaki, and S. Suzue, *Prog. Drug. Res.* **38**, 57 (1992) [*CA* **117**, 123,890 (1992)].
- 92MI151 O. N. Chupakhin, Yu. A. Azev, S. G. Alekseev, S. V. Shorshnev, E. Tsoi, and V. N. Charushin, *Mendeleev Commun.* 151 (1992) [*CA* **118**, 101,868 (1993)].
- 92RRC1307 E. Tighineanu and D. Raileanu, *Rev. Roum. Chim.* **37**, 1307 (1992) [*CA* **121**, 57,249 (1994)].
- 92SC2659 H. Z. Alkhathlan., *Synth. Commun.* **22**, 2659 (1992).
- 92T7601 D.St.C. Black, P. A. Keller, and N. Kumar, *Tetrahedron* **48**, 7601 (1992).
- 92WOP9206099 J. Segawa, M. Kitano, and Y. Tomii, *Pct. Int. WO* 92 06,099 (1992) [*CA* **117**, 131,180 (1992)].
- 93AJC843 D.St.C. Black, P. A. Keller, and N. Kumar, *Aust. J. Chem.* **46**, 843 (1993).
- 93AP427 M. Richter and G. Seitz, *Arch. Pharm.* **326**, 427 (1993) [*CA* **119**, 271,116 (1993)].
- 93GEP4128015 D. Jasserand, D. Paris, P. Demonchaux, M. Cottin, F. Floch, P. Dupassieux, and R. White, *Ger. Offen. DE* 4,128,015 (1993) [*CA* **119**, 139,255 (1993)].
- 93H1577 G. Cusmano, G. Macaluso, and M. Gruttadauria, *Heterocycles* **36**, 1577 (1993) [*CA* **120**, 77,262 (1994)].
- 93JAPK05117280 Y. Ito, H. Kato, S. Yasuda, T. Yoshida, and Y. Yamamoto, *Jpn. Kokai Tokkyo Koho JP* 05 117,280 (1993) [*CA* **119**, 271,733 (1993)].
- 93JAPK0559067 Y. Ito, H. Kato, S. Yasuda, T. Yoshida, and Y. Yamamoto, *Jpn. Kokai Tokkyo Koho JP* 05 59,067 (1993) [*CA* **119**, 139,204 (1993)].
- 93JAPK0570467 Y. Ito, H. Kato, S. Yasuda, T. Yoshida Y. Yamamoto, and M. Ueshima, *Jpn. Kokai Tokkyo Koho JP* 05 70,467 (1993) [*CA* **119**, 139,203 (1993)].
- 93JCS(CC)794 G. A. Hunter and H. McNab, *J. Chem. Soc., Chem. Commun.*, 794 (1993).
- 93JCS(P1)2087 J.-K. Shen, H. Katayama, N. Takatsu, and I. Shiro, *J. Chem. Soc., Perkin Trans. I*, 2087 (1993).

- 93JMC2621 Y. Jinbo, H. Kondo, Y. Inoue, M. Taguchi, H. Tsujishita, Y. Kotera, F. Sakamoto, and G. Tsukamoto, *J. Med. Chem.* **36**, 2621 (1993).
- 93JMC3148 Y. Jinbo, M. Taguchi, Y. Inoue, H. Kondo, T. Miyasaka, H. Tsujishita, F. Sakamoto, and G. Tsukamoto, *J. Med. Chem.* **36**, 3148 (1993).
- 93JPR397 K. Grohe, *J. Prakt. Chem. Chem.-Ztg.* **335**, 397 (1993) [*CA* **119**, 249,793 (1993)].
- 93MI11 S. H. Kim, J. U. Jeong, D. O. Choi, and K. J. Lee, *Bull. Korean Chem. Soc.* **14**, 11 (1993) [*CA* **119**, 95,287 (1993)].
- 93MI99 Y. A. Azev, S. V. Shorshnev, S. G. Alexeev, V. N. Charushin, and O. N. Chupakhin, *Mendeleev Commun.* **99** (1993) [*CA* **120**, 106,851 (1994)].
- 93MI107 D. G. Kim, S. V. Sokolova, V. V. Lukina, and S. A. Volkova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **36**, 107 (1993) [*CA* **120**, 244,808 (1994)].
- 93MI163 O. A. El-Sayed, M. A. El-Semary, and M. A. Khalil, *Alexandria J. Pharm. Sci.* **7**, 163 (1993) [*CA* **121**, 83,189 (1994)].
- 93MI273 H. S. Lin, A. A. Rampersaud, K. Zimmerman, M. L. Steinberg, and D. B. Boyd, *J. Chin. Chem. Soc.* **40**, 273 (1993).
- 93T8645 A. J. Blackman and C. Li, *Tetrahedron* **49**, 8645 (1993).
- 93WOP9322313 H. Mochizuki, K. Kato, I. Yamamoto, and K. Mizuguchi, *Pct. Int. WO* **93** 22,313 (1993) [*CA* **120**, 323,552 (1994)].
- 93WOP9325532 J. Segawa and Y. Makita, *Pct. Int. WO* **93** 25,532 (1993) [*CA* **120**, 270,140 (1994)].
- 94AP435 P. Gmeiner and J. Sommer, *Arch. Pharm.* **327**, 435 (1994).
- 94JAPK0616676 Y. Ito, H. Kato, S. Yasuda, N. Kato, T. Yoshida, and Y. Yamamoto, *Jpn. Kokai Tokkyo Koho JP* **06** 16,676 (1994) [*CA* **120**, 270,363 (1994)].
- 94JAPK0616677 Y. Ito, H. Kato, S. Yasuda, N. Kato, T. Yoshida, and M. Ueshima, *Jpn. Kokai Tokkyo JP* **06** 16,677 (1994) [*CA* **121**, 108,768 (1994)].
- 94JAPK0616678 M. Matsuoka and M. Matsuda, *Jpn. Kokai Tokkyo Koho JP* **06** 16,678 (1994) [*CA* **120**, 270,364 (1994)].
- 94M71 G. Santer and K. H. Ongania, *Monatsh. Chem.* **125**, 71 (1994).
- 94MI295 N. Rashed, E. I. Ibrahim, and E. S. H. El-Ashry, *Carbohydr. Res.* **154**, 295 (1994).
- 94MI311 W. Steinschifter and W. Stadlbauer, *J. Prakt. Chem./Chem.-Ztg.* **336**, 311 (1994) [*CA* **121**, 133,924 (1994)].
- 94TL2691 J. F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber, and K. Boukef, *Tetrahedron Lett.* **35**, 2691 (1994).
- 94TL9229 P. Kumar, C. U. Dinesh, and B. Pandey, *Tetrahedron Lett.* **35**, 9229 (1994).
- 94WOP9414819 J. Segawa, M. Matsuoka and Y. Tomii, *Pct. Int. WO* **94** 14,819 (1994) [*CA* **123**, 143,875 (1995)].
- 95AJC955 C. Li and A. J. Blackman, *Aust. J. Chem.* **48**, 955 (1995) [*CA* **123**, 52,650 (1995)].
- 95CPB63 J. Segawa, K. Kazuno, M. Matsuoka, I. Shirahase, M. Ozaki, M. Matsuda, Y. Tomii, M. Kitano, and M. Kise, *Chem. Pharm. Bull.* **43**, 63 (1995) [*CA* **123**, 256,564 (1995)].

- 95CPB1238 J. Segawa, K. Kazuno, M. Matsuoka, I. Amimoto, M. Ozaki, M. Matsuda, Y. Tomii, M. Kitano, and M. Kise, *Chem. Pharm. Bull.* **43**, 1238 (1995) [*CA* **124**, 8660 (1996)].
- 95CPB1678 K. Tsuji, H. Tsubouchi, and H. Ishikawa, *Chem. Pharm. Bull.* **43**, 1678 (1995).
- 95JAPK07112983 T. Hirota, Jpn. Kokai Tokkyo JP 07 112,983 (1995) [*CA* **123**, 143,895 (1995)].
- 95JMC669 D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck, and D. Jasserand, *J. Med. Chem.* **38**, 669 (1995).
- 95JOC2312 J. W. Dankwardt and L. A. Flippin, *J. Org. Chem.* **60**, 2312 (1995).
- 95WOP9504056 A. G. Romero, Pct. Int. WO 95 04,056 (1995) [*CA* **123**, 143,891 (1995)].
- 95WOP9514020 E. J. Jacobsen and R. E. Ten Brink, Pct. Int. WO 95 14,020 (1995) [*CA* **123**, 340,118 (1995)].
- 95ZOR447 Yu. A. Azev, S. V. Shorshnev, N. A. Klyuev, V. N. Charushin, and O. N. Chupakhin, *Zh. Org. Khim.* **31**, 447 (1995).
- 96EP700913 E. J. Glamkowski and B. S. Freed, Eur. Pat. EP 700,913 (1996) [*CA* **124**, 317,167 (1996)].
- 96HC555 S. Nakatsuka, D. Hu, and M. Tanahashi, *Heterocycl. Commun.* **2**, 555 (1996) [*CA* **126**, 171,742 (1997)].
- 96H2179 P. Beltrame, E. Cadoni, M. M. Carnasciali, G. Gelli, and A. Mugnoli, *Heterocycles* **43**, 2179 (1996) [*CA* **126**, 31,332 (1997)].
- 96IJC(B)1329 S. Kumari, S. Parkash, and V. K. Goel, *Indian J. Chem., Sect. B* **35**(B), 1329 (1996) [*CA* **126**, 18,768 (1997)].
- 96JCS(P1)675 S. Caddik, K. Aboutayab, K. Jenkins, and R. I. West, *J. Chem. Soc., Perkin Trans. 1*, 675 (1996).
- 96JCS(P1)1809 R. Consonni, P. D. Croce, R. Ferraccioli, and C. L. Rosa, *J. Chem. Soc., Perkin Trans. 1*, 1996 (1809).
- 96JLCR1087 R. F. Heier, M. W. Moon, W. T. Stolle, J. A. Easter, and R. S. P. Hsi, *J. Labelled Compound. Radiopharm.* **38**, 1087 (1996) [*CA* **126**, 131,442 (1997)].
- 96KFZ52 O. A. Yanborosova, T. M. Kon'shina, A. S. Zaks, A. I. Mikhalev, and M. E. Kon'shin, *Khim-Farm. Zh.* **30**, 52 (1996) [*CA* **125**, 75,750 (1996)].
- 96KG1252 D. G. Kim, A. V. Sashin, V. A. Kozlovskaya, and I. V. Andreeva, *Khim. Geterotsikl. Soedin.* 1252 (1996) [*CA* **126**, 89,297 (1997)].
- 96KG1510 L. Jukic, U. Bratusek, M. Skof, J. Svete, and B. Stanovnik, *Khim. Geterotsikl. Soedin.* 1510 (1996) [*CA* **126**, 251,363 (1997)].
- 96MI1457 M. Ozaki, J. Segawa, M. Kitano, Y. Tomii, T. Honmura, M. Matsuda, M. Kise, and T. Nishino, *Biol. Pharm. Bull.* **19**, 1457 (1996) [*CA* **126**, 29,023 (1997)].
- 96MI2775 C. W. Rees, D. G. Roe, and V. Thiery, *Chem. Commun. (Cambridge)* 2775 (1996) [*CA* **126**, 144,223 (1997)].
- 96PHA805 G. Dannhardt and A. Bauer, *Pharmazie* **51**, 805 (1996).
- 96T8471 D. Barret, H. Sasaki, T. Kinoshita, A. Fujikawa, and K. Sakane, *Tetrahedron* **52**, 8471 (1996).
- 96TL9403 J. P. Michael, C. B. de Koning, and T. V. Stanbury, *Tetrahedron Lett.* **37**, 9403 (1996).
- 96WOP9600217 J. Segawa, M. Matsuoka, and I. Amimoto, Pct. Int. WO 96 00,217 (1996) [*CA* **124**, 260,863 (1996)].

- 97CH609 A. I. Mikhalev, M. E. Kon'shin, and M. I. Vakhrin, *Chem. Heterocycl. Compd. (N.Y.)* **33**, 609 (1997) [*CA* **128**, 102,018 (1998)].
- 97EP807631 H. Takeshiba, C. Imai, H. Ohta, S. Kato, and H. Itoh, Eur. Pat. EP 807,631 (1997) [*CA* **128**, 34,691 (1998)].
- 97FRP2737206 S. Jegham, F. Puech, P. Burnier, and S. Cote des Combes, Fr. Demande FR 2,737,206 (1997) [*CA* **126**, 317,375 (1997)].
- 97H1979 G. Kim and G. Keum, *Heterocycles* **45**, 1979 (1997) [*CA* **128**, 3595 (1998)].
- 97H2395 P. Blurton, A. Brickwood, and D. Dhanak, *Heterocycles* **45**, 2395 (1997) [*CA* **128**, 270,523 (1998)].
- 97JHC969 A. Kutyrev and T. Kappe, *J. Heterocycl. Chem.* **34**, 969 (1997).
- 97JHC1773 M. Matsuoka, J. Segawa, Y. Makita, S. Ohmachi, T. Kashima, K. Nakamura, M. Hattori, M. Kitano, and M. Kise, *J. Heterocycl. Chem.* **34**, 1773 (1997).
- 97JMC639 R. F. Heier, L. D. Dolak, J. N. Duncan, D. K. Hyslop, M. F. Lipton, I. J. Martin, M. A. Mauragis, M. F. Piercey, N. F. Nichols, P. J. K. D. Schreur, M. W. Smith, M. W. Moon, *J. Med. Chem.* **40**, 639 (1997).
- 97JOC5630 B. B. Snider and T. Liu, *J. Org. Chem.* **62**, 6530 (1997).
- 97JOC6582 A. G. Romero, W. H. Darlington, and M. W. McMillan, *J. Org. Chem.* **62**, 6582 (1997).
- 97KFZ33 A. I. Mikhalev, M. E. Kon'shin, V. E. Kolla, F. Ya. Nazmetdinov, and M. I. Vakhrin, *Khim-Pharm. Zh.* **31**, 33 (1997) [*CA* **128**, 243,933 (1998)].
- 97OPP211 H. A. Abd El-Nabi, *Org. Prep. Proced. Int.* **29**, 211 (1997) [*CA* **126**, 305,553 (1997)].
- 97S773 T. C. Porter, R. K. Smalley, M. Teguiche, and B. Purwono, *Synthesis*, 773 (1997).
- 97T12765 B. Abarca, R. Ballesteros, and N. Houari, *Tetrahedron* **53**, 12,765 (1997).
- 97TL363 A. D. Patil, A. J. Freyer, R. Reichwein, B. Carte, L. B. Killmer, L. Faucette, and R. K. Johnson, *Tetrahedron Lett.* **38**, 363 (1997).
- 97TL3369 W. H. Pearson, N. S. Barta, and J. W. Kampf, *Tetrahedron Lett.* **38**, 3369 (1997).
- 97WOP9700074 D. B. Carter, Pct. Int. WO 97 00,074 (1997) [*CA* **126**, 171,597 (1997)].
- 98CHE828 K. G. Nazarenko, A. M. Demchenko, and V. A. Kovtunencko, *Chem. Heterocycl. Compd. (N.Y.)* **33**, 828 (1997) [*CA* **128**, 127,964 (1998)].
- 98H747 M.-C. Lallemand, M. Gaillard, N. Kunesch, and H.-P. Husson, *Heterocycles* **47**, 747 (1998) [*CA* **128**, 308,426 (1998)].
- 98JCS(P1)3851 K. Sasaki, A. Tsurumori, and T. Hirota, *J. Chem. Soc., Perkin Trans. 1*, 3851 (1998).
- 98JMC623 L. G. Hamann, R. I. Higuchi, L. Zhi, J. P. Edwards, X.-N. Wang, K. B. Marschke, J. W. Kong, L. J. Farmer, and T. K. Jones, *J. Med. Chem.* **41**, 623 (1998).
- 98MI763 K. Nishijima, T. Shinkawa, M. Ito, H. Nishida, I. Yamamoto, Y. Onuka, H. Inaba, and S. Miyano, *Eur. J. Med. Chem.* **33**, 763 (1998).
- 99JHC937 O. Cox, J. A. Prieto, L. Ramirez, M. Rodriguez, and J. R. Martinez, *J. Heterocycl. Chem.* **36**, 937 (1999).
- 99JHC675 A. R. Palma, J. Silva, E. Stashenko, J. R. Martinez, and V. Kouznetsov, *J. Heterocycl. Chem.* **36**, 675 (1999).

- 99JOC686 K. M. Werner, J. M. de los Santos, S. M. Weinreb, and M. Shang,  
*J. Org. Chem.* **64**, 686 (1999).
- 99JOC688 W. H. Pearson and Y. Ren, *J. Org. Chem.* **64**, 688 (1999).
- 99JOC5388 E. Fasani, F. F. Barberis Negra, M. Mella, S. Monti, and A. Albini,  
*J. Org. Chem.* **64**, 5388 (1999).
- 99JOC8263 J. F. Lui and C. H. Heathcock, *J. Org. Chem.* **64**, 8263 (1999).

# Organometallic Compounds of Chalcogenoazoles and Their Benzannulated Derivatives

ALEXANDER P. SADIMENKO

*Department of Chemistry, University of Fort Hare, 6 Chatham Road,  
Baysville, East London 5241, Republic of South Africa*

I. Introduction	192
II. Group VI and VII Metal Complexes	192
III. Group VIII Metal Complexes	195
A. Iron, Ruthenium, and Osmium	195
B. Cobalt, Rhodium, and Iridium	200
C. Nickel, Palladium, and Platinum	205
IV. Late Transition Metal Complexes	208
A. Copper, Silver and Gold	208
B. Mercury and Lanthanides	211
V. Conclusions	212
References	212

## Abbreviations

AN	acetonitrile
Bu	butyl
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
dppe	diphenylphosphinoethane
Et	ethyl
Me	methyl
nbd	2,5-norbornadiene
OTf	triflate
Ph	phenyl
Pr	propyl
tfb	tetrafluorobenzobarrelene
THF	tetrahydrofuran
THT	tetrahydrothiophene
Tol	tolyl

## I. Introduction

The organometallic chemistry of azoles containing chalcogen potential donor sites is not highly developed (99AHC1) compared to that of other heterocycles (e.g. (01AHC(78)1, C(79)115, C(80)157, C(81)167, 02AHC(83)117). In spite of this, the existing publications reveal the wide diversity of the coordination modes, including, alongside the expected N-coordination, X- (X = O, S, Se, Te) and C-coordination, mixed modes, carbene formation, and ring opening. Definitely, this group of ligands will attract the attention of future researchers and open additional possibilities. They could stem from the unique combination of the functions of the azole and five-membered heterocycles containing the chalcogen heteroatoms. Oxazole (95SRIMOC115) and isoxazole (88ZN(B)328) are characterized by predominant N-coordination. Predominance of the N-coordination in the thiazole complexes can be illustrated by numerous examples (88ICA(151)209, 90ICA(168)47, 91AX(C)1539, 92IC634, 92ICA(191)138). The O- (S-) coordination is less likely. There are however some indications of C-coordination. A special group of complexes incorporates metal carbenes, and the first metal carbenes of 1-methylthiazol-2-ylidene (97AGE1709) refer to 1968–1969 (68AGE950, 69AGE916).

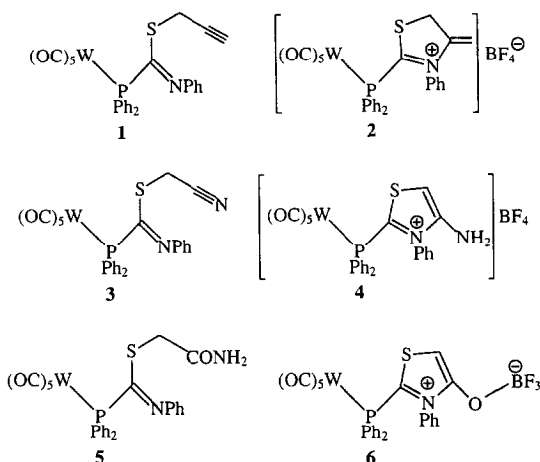
Oxazole (75JLAC533, 79JOC2042, 91JOC449,C3058) and thiazole (78TL5, 78TL9, 78TL13, 85TL5477, 88BCSJ3637) are lithiated to the 2-position. However, especially in the case of oxazole, the process is complicated by ring opening (97CB1213).

## II. Group VI and VII Metal Complexes

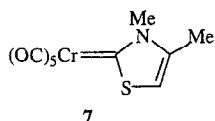
Thiazole with  $M(CO)_6$  gives N-coordinated complexes of composition  $[M(CO)_5L]$  ( $M = Cr, Mo, W$ ) (81IC2778). Thia(selena)diazole complexes of similar nature and composition are known (81ZN(B)172, 83CB230, 91JOM(405)309).

The C-coordinated thiazolium complexes are the result of the proton-induced cyclization reactions (98OM513). Thus, complex **1** on protonation with tetrafluoroboric acid yields the C-coordinated thiazolium structure **2**. In turn, the nitrile complex **3** under these conditions is transformed to the thiazolium cationic species **4**. Protonation of the amido complex **5** with tetrafluoroboric acid also results in a cyclization but it proceeds differently. The amino group of the  $CONH_2$  moiety is lost and  $BF_3$ -framework is coordinated via the carbonyl oxygen in an overall neutral complex **6**.

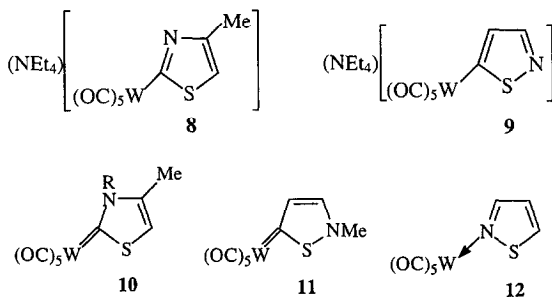




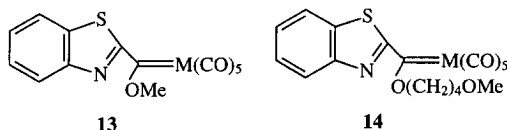
2-Chloro-3,4-dimethylthiazolium tetrafluoroborate with  $[Cr(CO)_5]^{2-}$  yields the neutral carbene complex **7** (74JCS(D)760).



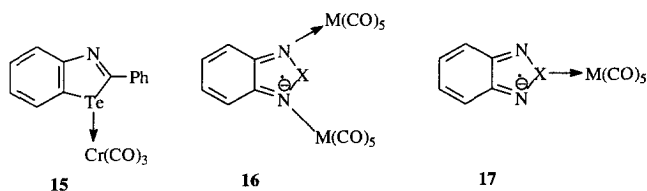
An alternative synthetic approach to the carbene derivatives of thiazole and isothiazole includes as the first step interaction of the lithium salts of these heterocycles with  $(NEt_4)[W(CO)_5Cl]$  which give the C-coordinated species **8** and **9** (75ICA(12)127, 95JCR(S)30). Further protonation of **8** with triflic acid or methylation with methyl triflate gives the carbene complexes **10** ( $R = H, Me$ ) (95JCR(S)30). For the isothiazole complex, alkylation gives the expected carbene **11** but protonation causes redistribution of the bonds and formation of the N-coordinated neutral isothiazole complex **12** but not N,S-coordinated as inferred previously (85OM275). The N-coordinated benzothiazole analogue is known (71JOM(30)89).



Lithium benzothiazolate with  $[M(CO)_6]$  ( $M = Cr, Mo, W$ ) and subsequently with methyl triflate in THF gives a mixture of the carbenes **13** ( $M = Cr, W$ ) and **14** ( $M = Cr, Mo, W$ ) (99JOM(590)158). The latter reaction run in methylene chloride affords only **13** ( $M = Cr, W$ ).

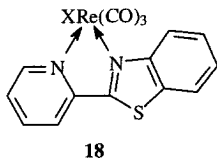


X-ray analysis shows that the coordination via the tellurium atom in the benzotellurazole ligand is possible, as in **15** (93AHC47, 96KK376, 96KK512). Such a coordination mode may be related to a high donor activity of the tellurium atom (96ZNK1297). The reduced 2,1,3-benzochalcogenodiazoles react with Group VI metal hexacarbonyls differently forming in majority of the cases ( $M = Cr, Mo$ ;  $X = O, S, Se$ ;  $M = W, X = O, S$ ) the N,N-coordinated products **16** through the stage of the mono-N-coordinated species (82AGE700). However, when  $M = W$  and  $X = Se$ , the Se-coordinated complex **17** results.

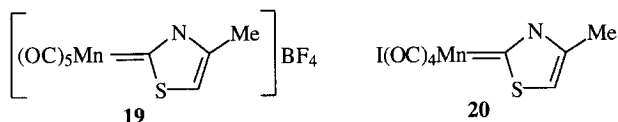


4,5-Disubstituted 1,2,3-selenadiazoles react with  $[(\eta^5-Cp)Mo(CO)_2]_2$  to form a series of ring-opened and finally deselenated products (92JA5467).

2-(2'-Pyridyl)benzothiazole with  $[Re(CO)_5X]$  ( $X = Cl, Br$ ) forms the chelate structures **18** ( $X = Cl, Br$ ) (01ICA(314)91). With silver triflate, dehalogenation occurs followed by formation of **18** ( $X = OTf$ ). The latter refluxed in acetonitrile gives the cationic complex of stoichiometry  $[Re(CO)_3L(AN)](OTf)$ .



2-Chloro-3,4-dimethylthiazolium tetrafluoroborate with  $[Mn(CO)_5]^-$  gives the carbene complex **19** (74JCS(D)760). The product reacts with tetraethylammonium iodide to give the *cis*-neutral complex **20**.

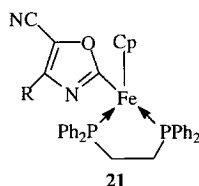


Complex  $[\text{Re}(\text{CO})_2(\text{PPh}_3)_2\text{L}]$  [L is the anion of 2-(methylamino)thiazole] (85TMC413, 87JCS(D)2299) has an interesting reactivity pattern. Thus, with the heterocumulene *p*-TolNCS it forms the formamido complex of rhenium(I)  $[\text{Re}(\text{CO})_2(\text{PPh}_3)_2\{\text{O}-\text{C}(\text{NHTol-}p)=\text{S}\}]$  through the stages of the mono- and dithiocarbamate complexes (87JCS(D)2299). With PhNCS, the thiazolyl thioureido species  $[\text{Re}(\text{CO})_2(\text{PPh}_3)_2(\text{SC}(\text{NPh})\text{NMe}(\text{C}_3\text{H}_2\text{NS}))]$  results (88JCS(D)899).  $\text{CS}_2$  in these conditions gives the thiocarbamate derivative  $[\text{Re}(\text{CO})_2(\text{PPh}_3)_2(\text{S}_2\text{CNMe}(\text{C}_3\text{H}_2\text{NS}))]$ . In both cases, insertion reactions into the Re–N(amino) bond takes place. In the thioureido species, the nitrogen heteroatom of the thiazolyl framework is the participant of the coordination unit, while in the thiocarbamate complex the thiazolyl heteroatoms do not serve as the donor sites. The lithium salt of *N*-*ortho*-hydroxybenzylidene-2-thiazolylimine reacts with  $[\text{M}(\text{PPh}_3)_2(\text{CO})_3\text{Cl}]$  ( $\text{M} = \text{Re}, \text{Tc}$ ) to yield  $[\text{M}(\text{PPh}_3)_2(\text{CO})_2((\text{C}_3\text{H}_2\text{NS})\text{N}=\text{CHC}_6\text{H}_4\text{O})]$ , where the thiazolyl ring does not participate in coordination (89ICA(160)23). The complexes with 2-mercaptobenzothiazole (L),  $[\text{M}(\text{CO})_3(\text{L})]$  ( $\text{M} = \text{Mn}, \text{Re}$ ), with the S,N-coordination and the ligand in the thione form are known (76TMC195). This coordination mode was also noted in the related compounds (74IC225, 76JCS(CC)743).

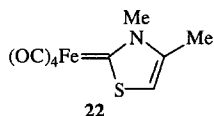
### III. Group VIII Metal Complexes

#### A. IRON, RUTHENIUM, AND OSMIUM

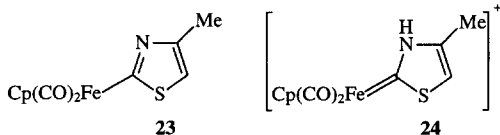
The case of C-coordinated oxazole, **21**, was reported in organoiron chemistry (89JOM(372)287). Another example involves the interaction of the cyano complexes  $[\text{M}(\text{CN})(\text{Cp})(\text{dppe})]$  ( $\text{M} = \text{Fe}, \text{Ru}$ ) or  $[(\eta^5\text{-Cp})\text{Fe}(\text{dppe})(\text{CNH})]\text{Br}$  with *gem*-dicyanoepoxide to afford the oxazol-2-yl complexes with the C-coordination mode (96JCS(D)3231).



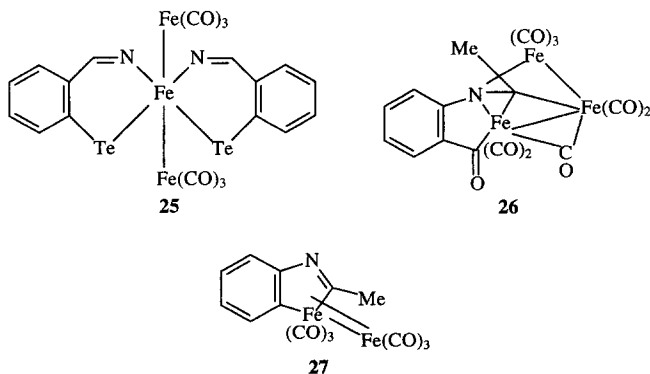
2-Chloro-3,4-dimethylthiazolium tetrafluoroborate reacts with  $[\text{Fe}(\text{CO})_4]^{2-}$  to yield the neutral carbene complex **22** (74JCS(D)760). 1-Methyl-2-chlorobenzothiazolium tetrafluoroborate with  $\text{Na}_2[\text{Fe}(\text{CO})_4] \cdot \text{dioxane}$  gives the similar neutral carbene complex (75JCS(D)939).



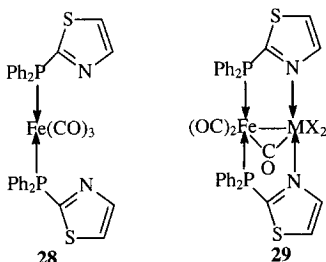
Lithium 4-methylthiazolate and benzothiazolate with  $[(\eta^5\text{-Cp})\text{Fe}(\text{CO})_2\text{Cl}]$  form the C-coordinated complexes, e.g. **23**, which on protonation with triflic acid transform into the carbenes, e.g. **24** (92JCS(D)1009). Isothiazole enters the same chain of reactions but can also be methylated using methyl triflate (94JOM(479)C12).



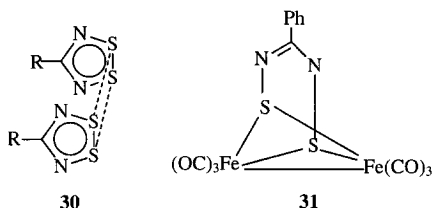
Organoiron chemistry of benzotellurazoles is of interest (97OM3194). Thus, benzoisotellurazole with  $\text{Fe}_3(\text{CO})_{12}$  yields the product of ring-opening **25**, while 2-methylbenzotellurazole gives two products of detelluration **26** and **27**. Similar trend can be noted for bezothia(selena)diazoles, which on reaction with iron carbonyls experience the ring opening and give rise to  $\alpha$ -thia- (selena-) keto carbene species (72JCS(P1)2165, 73JA2501, 80AGE632) as well as to the ketene (80AGE632), imine (83OM560), and hydrazonato (89OM2961) complexes.



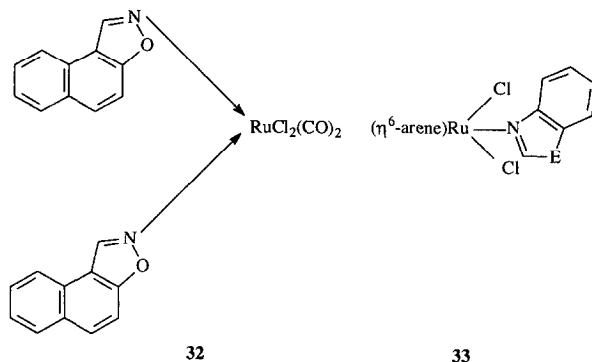
2-(Diphenylphosphino)thiazole with iron pentacarbonyl in the presence of sodium hydroxide gives the P-coordinated product **28** (99JOM(575)51). The latter retains the ligating properties and with mercury(II) thiocyanate or cadmium(II) iodide gives the N,P-coordinated species **29** (M = Hg, X = SCN; M = Cd, X = I) containing the iron-mercury (cadmium) bond and one bridging carbonyl group.



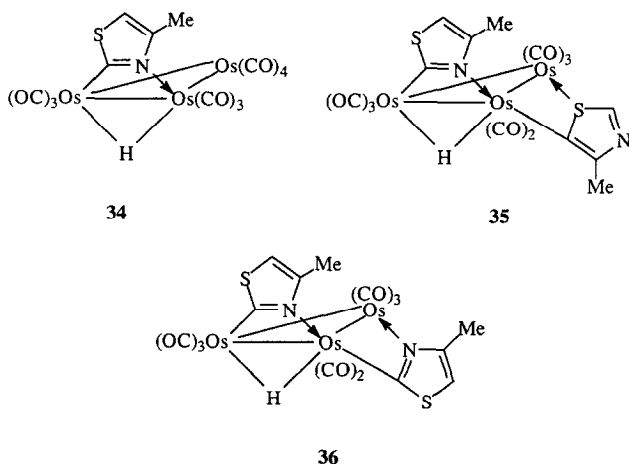
1,2,3,5-Dithiadiazole is known in three stable states of oxidation: six  $\pi$ -electron cation, seven  $\pi$ -electron neutral radical, or eight  $\pi$ -electron anion (92MI1, 92MI2, 95AHC137, 96IC4264). A series of iron cluster complexes of 1,2,3,5-dithiadiazole are known,  $[\text{Fe}_2(\text{CO})_6(\text{S}_2\text{N}_2\text{CC}_6\text{H}_4\text{X})]$  (X = H, OMe,  $\text{CF}_3$ ). However, this formulation had to be revised on the basis of the electrochemical and ESR data in favor of the diamagnetic products  $[\text{Fe}_2(\text{CO})_6(\text{S}_2(\text{NH})\text{NCC}_6\text{H}_4\text{X})]$  (X = H, OMe,  $\text{CF}_3$ ) (94PSS449). This class of ligands is described as stable free radicals that reveal a tendency to dimerize, for example under atomic nitrogen (87JCS(CC)63, 89JCS(D)1705, 90JCS(D)2793) to yield **30** (R = Ph, *p*- $\text{ClC}_6\text{H}_4$ ). The dimer (R = Ph) with  $[\text{Fe}_2(\text{CO})_9]$  or  $[\text{Fe}_3(\text{CO})_{12}]$  gives the ring-opened product **31** (89JCS(D)2229). Species  $[\text{Ni}(\eta^5\text{-Cp})(\text{CO})]_2$  forms the product with the identical arrangement (91JCS(D)1105).



Naphthisoazole and 2-aminobenzothiazole with  $[\text{RuCl}_2(\text{CO})_2]_n$  form products of stoichiometry  $[\text{RuCl}_2(\text{CO})_2\text{L}_2]$ , where the ligands are classically coordinated via the pyridine-type nitrogen atom of the heteroring, e.g. **32** (88POL219). Benzoxazole or benzothiazole and  $[(\eta^6\text{-arene})\text{RuCl}_2]_2$  (arene =  $\text{MeC}_6\text{H}_4\text{Pr}^i\text{-}p$ ,  $\text{C}_6\text{Me}_6$ ) form the N-coordinated products **33** (E = O, S; arene =  $\text{MeC}_6\text{H}_4\text{Pr}^i\text{-}p$ ,  $\text{C}_6\text{Me}_6$ ) (00EJI29).

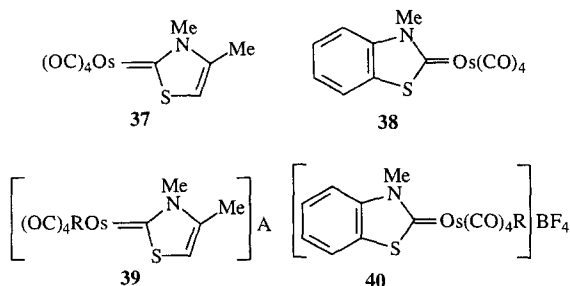


The Group VIII cluster chemistry of the thiazole ring is known (93JOM(459)271). Thus, 4-methylthiazole (LH) reacts with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  to yield  $[\text{Os}_3(\mu\text{-H})(\text{CO})_{10}(\mu\text{-}2,3\text{-}\eta^2\text{-L})]$ , **34**, in which thiazole is bridged to the cluster via the nitrogen and carbon atoms of the  $\text{N}=\text{C}$  bond (96JCS(D)1731). With triphenylphosphine, the products of substitution of one and two carbonyl groups at different osmium sites result, and they represent complex mixtures of isomers. Heating **34** with excess 4-methylthiazole yields a mixture of **35** and **36**, and a rare feature of S-coordination is observed in **35**.  $[\text{Ru}(\text{CO})_3]$  in these conditions yields the analogue of **34** and in excess 4-methylthiazole only the C,N-coordinated product of type **36**.

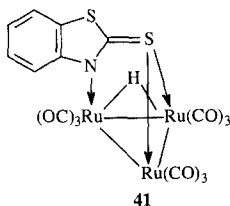


2-Chloro-3,4-dimethylthiazolium tetrafluoroborate and 3-methyl-2-chlorobenzo-thiazolium tetrafluoroborate and  $[\text{Os}_3(\text{CO})_{12}]$  in the presence of sodium in liquid ammonia give the neutral carbene complexes **37** and

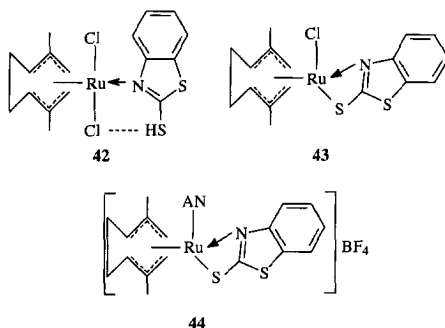
**38**, respectively (75JCS(D)939). The same thiazolium salts but with  $\text{Na}_2[\text{Ru}(\text{CO})_4]$  yield similar ruthenium neutral carbene species. The osmium complex **37** undergoes  $\text{CO}/\text{PPh}_3$  ligand substitution to give the  $(\text{CO})_3(\text{PPh}_3)$ -product. Both **37** and **38** undergo oxidative addition with tetrafluoroboric acid and yield **39** ( $\text{R}=\text{H}$ ,  $\text{A}=\text{BF}_4$ ) and **40** ( $\text{R}=\text{H}$ ), respectively. Triethylamine readily regenerates **37** and **38**. The hydrido complex **39** ( $\text{R}=\text{H}$ ,  $\text{A}=\text{PF}_6$ ) also results from **37** and nitrosonium hexafluorophosphate in methanol and toluene. Complexes **37** and **38** also react with trimethyloxonium tetrafluoroborate and yield the osmium(II) complexes containing the osmium-methyl framework, **39** ( $\text{A}=\text{BF}_4$ ,  $\text{R}=\text{Me}$ ) and **40** ( $\text{R}=\text{Me}$ ).



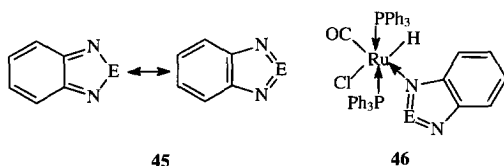
2-Mercaptobenzothiazole with  $[\text{Ru}_3(\text{CO})_{12}]$  gives the cluster **41** (76TMC186, C192, 78IC2103). Two ruthenium atoms are bonded to the exocyclic sulfur site, while the third one is coordinated via the nitrogen heteroatom.



2-Mercaptobenzothiazole with  $[\text{Ru}(\eta^3:\eta^3\text{-C}_{10}\text{H}_{16})(\mu\text{-Cl})\text{Cl}]_2$  ( $\text{C}_{10}\text{H}_{16}$  is 2,7-dimethylcyclooctadienyl) gives complex **42** with a monodentate coordination of the heteroaromatic ligand through the pyridine nitrogen atom and intramolecular  $\text{Cl}\cdots\text{HS}$  hydrogen bond (91JCS(D)1563). In solution, hydrogen chloride is released, and the chelate structure **43** is formed. In acetonitrile in the presence of silver tetrafluoroborate, the transformation of **43** to the cationic species **44** takes place.



2,1,3-Benzochalcogenodiazoles have some extent of the  $N=E=N$  linkage attenuated by the conjugation with the benzene ring, as in **45** ( $E = S, Se$ ) (89JOM(377)151, 90JCS(D)1737). 2,1,3-Benzothiadiazole and 2,1,3-benzoselenadiazole both react with  $[RuClH(CO)(PPh_3)_3]$  to yield the products **46** ( $E = S, Se$ ). With alkynes and alkynols, complexes **46** ( $E = S, Se$ ) derivatize to the vinyl species  $[Ru(CH=CHR)Cl(CO)L(PPh_3)_2]$  ( $R = H, C_6H_4Me-4$ ;  $L = 2,1,3$ -benzothiadiazole and 2,1,3-benzoselenadiazole) (91OM3903, 92 JOM(438)209). Osmium analogues are synthesized differently (98JCS (D)3501). Heating 2,1,3-benzothiadiazole (**L**) with  $[OsH(CO)(AN)_2(PPh_3)_2](ClO_4)$  in the presence of excess tetraethylammonium chloride gives  $[OsH(CO)(Cl)(L)(PPh_3)_2]$ . With ethyne or 4-ethynyltoluene and then ethanol the alkenyl products  $[Os(CH=CHR)Cl(CO)(L)(PPh_3)_2]$  ( $R = H, C_6H_4Me-4$ ) are formed. With the diyne  $(C \equiv CC_6H_4Me-4)_2$ , the ethynyl complex  $[Os\{C(C \equiv CC_6H_4Me-4)=CHC_6H_4Me-4\}Cl(CO)(L)(PPh_3)_2]$  follows.



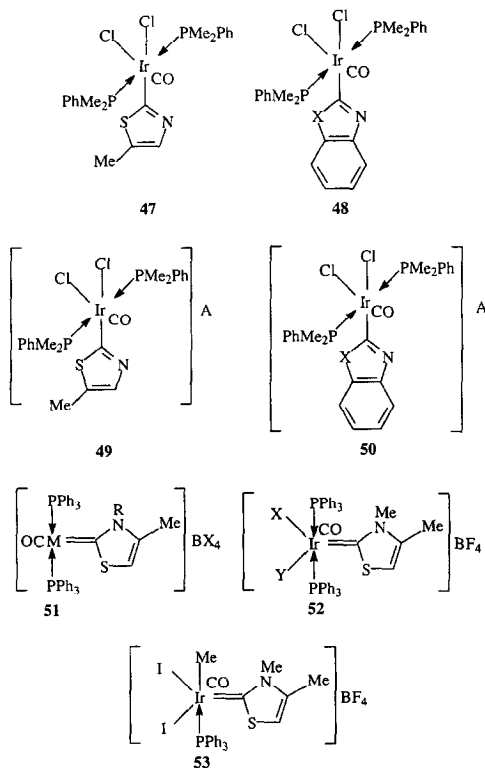
## B. COBALT, RHODIUM, AND IRIIDIUM

Reaction of 1,2,3-selenadiazoles with  $[(\eta^5-C_5R_5)Co(CO)_2]$  ( $R = H, Me$ ) yields not the molecular complexes but the diselenols with the general formula  $[Co(C_5R_5)(-Se-C(R')=C(R')-Se)]$  where  $R' = H, (CH_2)_6, -CH=CH-(CH_2)_4, H_2C=CH-CH_2, Ph$  (93JCS(D)703). Other reactions of this nature include  $[(\eta^5-C_5R_5)Co(PPh_3)_2]$  (89OM800, 92HC87, 93JOM(444)219).

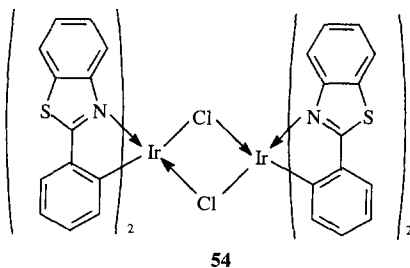
2-Chloro-5-methylthiazole, 2-chlorobenzothiazole, and 2-chlorobenzoxazole oxidatively add to  $[IrCl(CO)(PMe_2Ph)_2]$  to yield the neutral iridium(III) carbene species **47** and **48** ( $X = O, S$ ) (73JOM(50)C54,



74JCS(D)102). The products are protonated by perchloric or tetrafluoroboric acid to the cationic carbenes **49** ( $R = H$ ;  $A = ClO_4, BF_4$ ) and **50** ( $X = O, S$ ;  $A = ClO_4, BF_4$ ). Oxidative addition of 2-chloro-3,4-dimethylthiazolium tetrafluoroborate to  $[IrCl(CO)(PMe_2Ph)_2]$  gives the carbene complex **49** ( $R = Me$ ,  $A = BF_4$ ). 2-Chlorothiazolium tetrafluoroborates with  $[M(CO)_{4-n}(PPh_3)_n]^+$  ( $M = Ir$ ,  $n = 1$ ;  $M = Rh$ ,  $n = 2$ ) give the cationic  $\sigma$ -complexes **51** ( $M = Ir$ ,  $Rh$ ,  $R = Me$ ,  $X = F$ ;  $M = Ir$ ,  $R = Et$ ,  $X = Ph$ ) (74JCS(D)760). In the latter case, when  $X = Ph$  excess sodium tetraphenylborate is employed. Complex **51** ( $M = Ir$ ,  $R = Me$ ,  $X = F$ ) oxidatively adds molecular hydrogen, chlorine, and iodine, as well as hydrogen chloride, to afford the iridium(III) products **52** ( $X = Y = H$ ,  $Cl$ ,  $I$ ;  $X = H$ ,  $Y = Cl$ ). Complex **52** ( $X = H$ ,  $Y = Cl$ ) also follows from the reaction of **51** ( $M = Ir$ ,  $R = Me$ ,  $X = F$ ) with lithium chloride in ethanol. Lithium bromide in similar conditions gives **52** ( $X = H$ ,  $Y = Br$ ). Complex **51** ( $M = Ir$ ,  $R = Me$ ,  $X = F$ ) also reacts with sodium borohydride in methanol to yield **52** ( $X = Y = H$ ). The reaction with methyl iodide is interesting. It leads to the neutral iridium(III) species **53** probably through the formation of **52** ( $X = Me$ ,  $Y = I$ ).

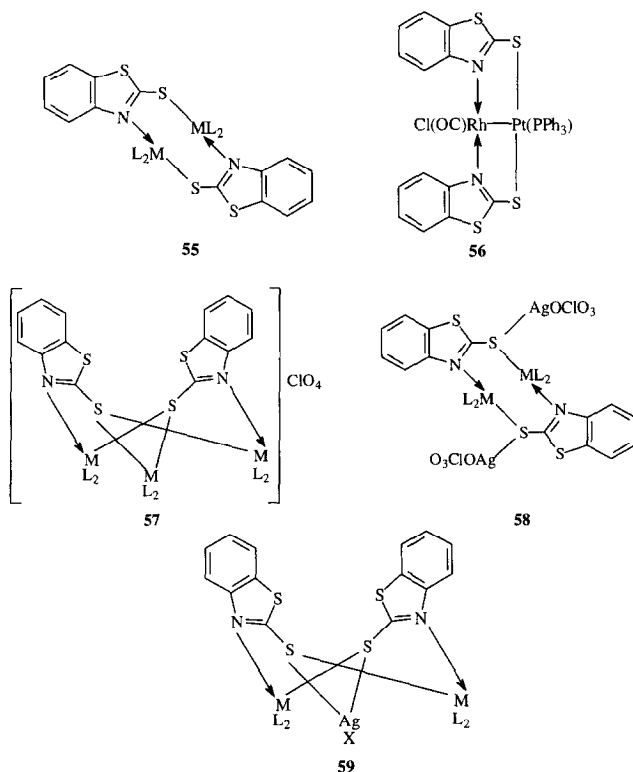


2-Phenyl- and 2-naphthylbenzothiazole with iridium(III) chloride give cyclometallated derivatives of the type **54** containing two chloride bridging ligands (01IC1704).



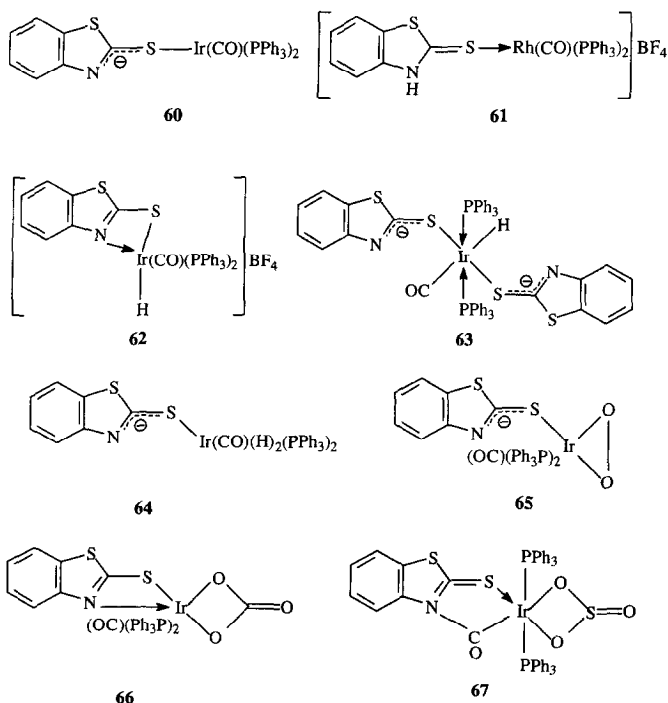
Lithium benzothiazole-2-thiolate with  $[(\eta^4\text{-cod})\text{RhCl}]_2$  gives complex **55** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = \text{cod}$ ) (86JCS(CC)1737). Further carbonylation and then CO/ $\text{PPh}_3$  ligand substitution leads to **55** [ $\text{M} = \text{Rh}$ ,  $\text{L}_2 = (\text{CO})(\text{PPh}_3)$ ] (89JCS(D)25). The product reacts with  $[(\eta^4\text{-cod})\text{PtCl}_2]$  to afford an unusual dinuclear product **56** (92IC969). 2-Mercaptobenzothiazole protonates the methoxy moiety in  $[\text{Ir}(\mu\text{-MeO})(\eta^4\text{-cod})]_2$  to yield species **55** ( $\text{M} = \text{Ir}$ ,  $\text{L}_2 = \text{cod}$ ) (91JCS(D)255). Further interaction with  $[\text{Ir}(\eta^4\text{-cod})(\text{Me}_2\text{CO})_2]\text{ClO}_4$  gives the trinuclear species **57** ( $\text{M} = \text{Ir}$ ,  $\text{L}_2 = \text{cod}$ ). Reaction of the neutral bridging complexes **55** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = \text{cod}$ , nbd, tfb) with  $[\text{RhL}_2(\text{Me}_2\text{CO})_x]\text{ClO}_4$  ( $\text{L}_2 = \text{cod}$ , nbd, tfb) gives the trinuclear species **57** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = \text{cod}$ , nbd, tfb) with the  $\mu_3$ -bridging function of the benzothiazole-2-thiolato ligand (86JCS(CC)1737, 86NJC75, 87AGE444, 90JCS(D)1493). Bubbling carbon monoxide through the solutions of **57** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = \text{cod}$ , nbd, tfb) gives **57** ( $\text{M} = \text{Rh}$ ,  $\text{L} = \text{CO}$ ). Triphenylphosphine causes substitution of the half of carbon monoxide ligands and formation of **57** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = (\text{CO})(\text{PPh}_3)$ ). Complexes **55** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = (\text{CO})(\text{PPh}_3)$ , tfb) react with  $[\text{RhL}_2(\text{Me}_2\text{CO})_x]\text{ClO}_4$  ( $\text{L}_2 = \text{cod}$ , nbd, tfb,  $(\text{CO})_2$ ) or  $[\text{Rh}(\mu\text{-Cl})\text{L}_2]_2$  ( $\text{L}_2 = \text{cod}$ , nbd, tfb,  $(\text{CO})_2$ ) in the same fashion to give the mixed-ligand analogues of **57** ( $\text{M} = \text{Rh}$ ), namely the  $(\text{CO})_2(\text{PPh}_3)_2\text{L}_2$  ( $\text{L}_2 = \text{cod}$ , nbd, tfb,  $(\text{CO})_2$ ) and  $(\text{tfb})_2\text{L}_2$  ( $\text{L}_2 = (\text{CO})_2$ ,  $(\text{CO})(\text{PPh}_3)$ ) complexes. The dinuclear complex **55** ( $\text{M} = \text{Rh}$ ,  $\text{L}_2 = (\text{CO})(\text{PPh}_3)$ ) reacts with  $[(\eta^4\text{-cod})\text{Ir}(\text{Me}_2\text{CO})_2]\text{ClO}_4$  and  $[(\eta^3\text{-C}_3\text{H}_5)\text{Pd}(\text{Me}_2\text{CO})_2]\text{ClO}_4$  to give the heterotrinuclear products of the type **57**,  $[(\text{Rh}(\mu_3\text{-C}_7\text{H}_4\text{NS}_2)(\text{CO})(\text{PPh}_3))_2\text{ML}'_2]$  ( $\text{ML}'_2 = \text{Ir}(\eta^4\text{-cod})$ ,  $\text{Pd}(\eta^3\text{-C}_3\text{H}_5)$ ) (91JCS(D)255). The same starting complex forms the 1:2 adduct with silver perchlorate,  $[(\text{Rh}(\mu_3\text{-C}_7\text{H}_4\text{NS}_2)(\text{CO})(\text{PPh}_3))_2 \cdot 2\text{AgClO}_4]$ , which on the basis of the spectroscopic data was assigned the structure **58**. Both rhodium and iridium  $\eta^4\text{-cod}$  complexes **55** ( $\text{M} = \text{Rh}$ ,  $\text{Ir}$ ;  $\text{L}_2 = \text{cod}$ ) form with silver perchlorate the 1:1 adducts **59** ( $\text{M} = \text{Rh}$ ,  $\text{Ir}$ ;  $\text{L}_2 = \text{cod}$ ;  $\text{X} = \text{OClO}_3$ ), where

the metalloligands are bidentate and chelating with respect to the  $\text{AgOClO}_3$  fragment. Similar reactions take place between the  $\eta^4\text{-cod}$  rhodium and iridium precursors,  $[(\eta^4\text{-cod})\text{MCl}]_2$ , and silver chloride, nitrate, and tetrafluoroborate ( $\text{L}_2 = \text{cod}$ ;  $\text{M} = \text{Rh}$ ,  $\text{X} = \text{Cl}$ ,  $\text{ONO}_2$ ,  $\text{BF}_4$ ;  $\text{M} = \text{Ir}$ ,  $\text{X} = \text{Cl}$ ). Complexes **55** ( $\text{M} = \text{Rh}$ ,  $\text{Ir}$ ;  $\text{L}_2 = \text{cod}$ ) also react with  $[\text{Ag}(\text{PPh}_3)(\text{Me}_2\text{CO})_x]\text{ClO}_4$  and give the heterotrinnuclear cationic products of the structure similar to **57**,  $[(\eta^4\text{-cod})_2\text{M}_2(\mu_3\text{-C}_7\text{H}_4\text{NS}_2)\text{Ag}(\text{PPh}_3)]\text{ClO}_4$  ( $\text{M} = \text{Rh}$ ,  $\text{Ir}$ ). The heterotrinnuclear aggregates of the structural pattern **59** are also obtained on the reaction between the same precursors and  $\text{CuCl}$  or  $[\text{AuCl}(\text{THT})]$  yielding  $[(\eta^4\text{-cod})_2\text{M}_2(\mu_3\text{-C}_7\text{H}_4\text{NS}_2)\text{M}'\text{Cl}]$  ( $\text{M} = \text{Rh}$ ,  $\text{Ir}$ ;  $\text{M}' = \text{Cu}$ ,  $\text{Au}$ ).



Lithium benzothiazole-2-thiolate with  $[\text{IrCl}(\text{CO})(\text{PPh}_3)_2]$  gives the square-planar mononuclear species **60** (94JOM(469)C31, 95OM4764). The rhodium analog is also known (88OM1939, 90OM12, 91OM3906). Protonation of the rhodium and iridium analogs follows opposite patterns. Thus, the rhodium complex is protonated by the tetrafluoroboric acid at the nitrogen site, and the mononuclear nature of the rhodium(I) species is retained, **61**

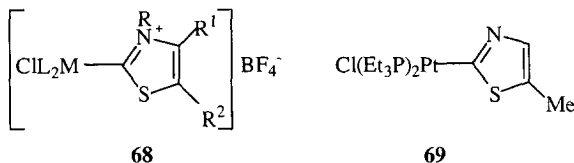
(93JOM(455)225). Iridium complex **60** in these conditions is transformed into the iridium(III) species **62** with the change of the coordination mode of benzothiazole-2-thiolate moiety to the  $\eta^2(\text{S}, \text{N})$  type (95OM4764). 2-Mercaptobenzothiazole oxidatively adds to the iridium species **60** forming the iridium(III) species with the iridium-hydride bond and two monodentately coordinated benzothiazole-2-thiolate ligands, **63**. The latter is protonated with tetrafluoroboric acid with elimination of the thiolate ligand and formation of **62**. Oxidative addition of methyl iodide leads to elimination of both heterocyclic ligands and formation of  $[\text{IrI}_2\text{Me}(\text{CO})(\text{PPh}_3)_2]$ . When molecular hydrogen adds oxidatively to **60**, the mononuclear nature of the complex **60** is retained and the iridium(III) product **64** is formed. Molecular oxygen and **60** produce the peroxo complex **65**. The product undergoes further oxidation with water to yield the carbonate species **66** characterized by re-switch of the coordination mode of the heteroaromatic counterpart. Sulfur dioxide reacts with the peroxo species **65** in a most unusual fashion giving the sulfate complex **67**, in which the CO ligand is formally inserted into the metal-nitrogen bond. In the tetranuclear species  $[\text{Ir}_4(\mu\text{-C}_7\text{H}_4\text{NS}_2)_4]\text{I}_2(\text{CO})_8$ , the ligand plays a role of a bridge that links each couple of iridium atoms via the N- and S-sites (88AGE402).



Reaction of the diphosphine ligand  $R_2P(CH_2)_2PR_2$  ( $R$  = benzothiazolyl) (L) with  $[RhCl(PPh_3)_3]$  gives the exclusively P-coordinated product  $[RhCl(PPh_3)(L)]$  (88JOM(338)C31, 92JCS(D)241), which is perhaps a common feature of the P-substituted derivatives of oxazole and thiazole.

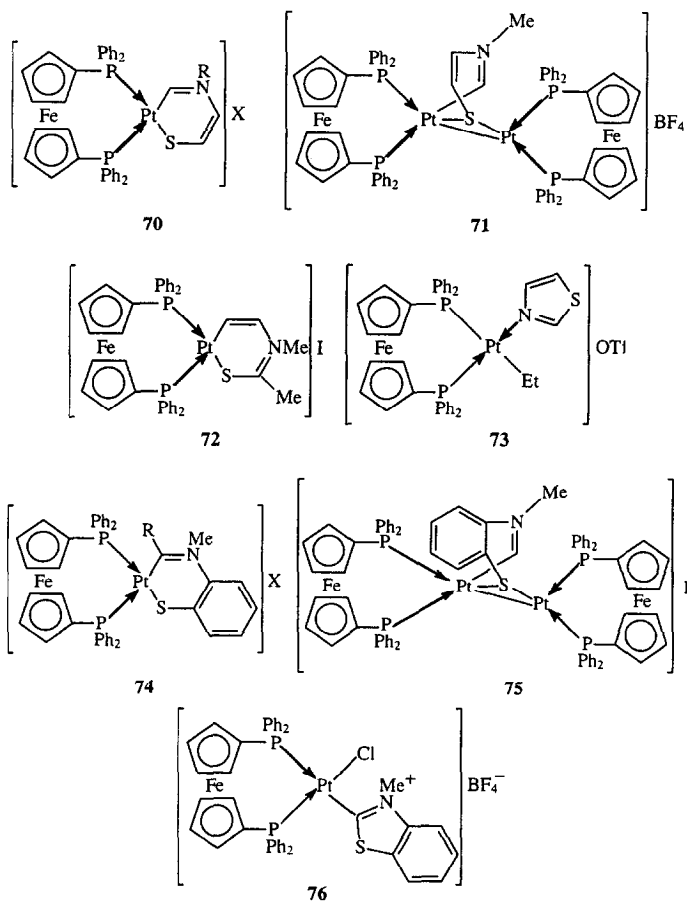
### C. NICKEL, PALLADIUM, AND PLATINUM

The N-coordinated derivatives are quite rare in organopalladium chemistry but are observed for some complexes of 2-phenyloxazolones (97ZN(B)1199). 2-Chloro-3,4-dimethylthiazolium tetrafluoroborate oxidatively adds to a number of the derivatives of the nickel group,  $[Ni(PPh_3)_4]$ ,  $[Pd(PPh_3)_4]$ ,  $[Pd(PMePh_2)_4]$ ,  $[Pt(PMePh_2)_4]$ ,  $[Pt(PEt_3)_2(PhCH=CHPh)]$  and gives the corresponding cationic carbene derivatives **68** ( $R = R^1 = Me$ ;  $R^2 = H$ ;  $M = Ni$ ,  $L = PPh_3$ ;  $M = Pd$ ,  $L = PPh_3$ ,  $PMePh_2$ ;  $M = Pt$ ,  $L = PEt_3$ ,  $PMePh_2$ ) (74JCS(D)102). Alternatively, 2-chloro-5-methylthiazole with  $[Pt(PEt_3)_2(PhCH=CHPh)]$  first gives the C-coordinated  $\sigma$ -complex **69**, and then on protonation with tetrafluoroboric acid—the cationic carbene **68** ( $R = R^1 = H$ ,  $R^2 = Me$ ,  $M = Pt$ ,  $L = PEt_3$ ).

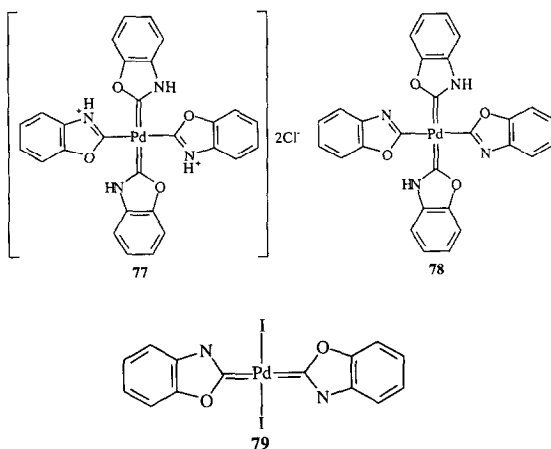


3-Methylthiazolium tetrafluoroborate reacts with 1,1'-bis(diphenylphosphino)ferrocene- $\eta^2$ -etheneplatinum to give the insertion product **70** ( $R = Me$ ,  $X = BF_4$ ) formed by the ring-opening of the thiazolium heterocycle (94JA5180). With excess platinum species, another insertion product **71** is formed. 2,3-Dimethylthiazolium iodide gives a single insertion product **72**. The parent thiazolium triflate gives **70** ( $R = H$ ,  $X = OTf$ ), the N-coordinated **73** and a trace amount of the unidentified product. 3-Methylbenzothiazolium iodide gives the 1:1 and 1:2 C,S-insertion products **74** ( $R = H$ ,  $X = I$ ) and **75** similar to **70** and **71**. From 2,3-dimethylbenzothiazolium tetrafluoroborate, only **74** ( $R = Me$ ,  $X = BF_4$ ) is formed. 2-Chloro-3-methylbenzothiazolium tetrafluoroborate also forms **74** ( $R = Cl$ ,  $X = BF_4$ ) but this product experiences a remarkable rearrangement

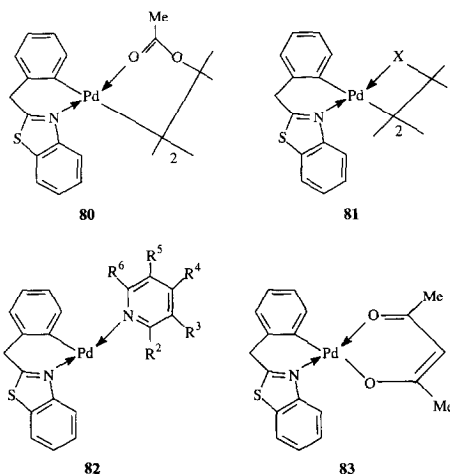
to the platinum-chloride complex **76** where the benzothiazolium ligand is  $\eta^1(\text{C})$ -coordinated.



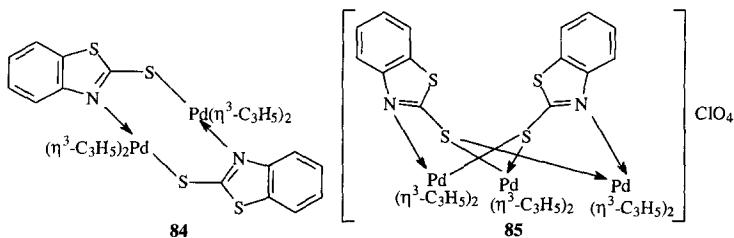
2-Trimethylsiloxyphenyl isocyanide enters the cyclization reaction with  $[\text{MCl}_2(\text{NCPh})_2]$  ( $\text{M} = \text{Pt}, \text{Pd}$ ) to yield the homoleptic tetracarbenes **77** ( $\text{M} = \text{Pt}, \text{Pd}$ ) (97JOM(541)51). Complex **77** ( $\text{M} = \text{Pd}$ ) enters an interesting reaction with ammonia to yield the species **78** where two of this benzoxazol-2-ylidene ligands are deprotonated and become C-coordinated benzoxazole moieties, while the other two remain intact. Palladium(II) iodide in these conditions behaves differently yielding the di-*iso*-cyanide complex, which in the presence of tetra-*n*-butyl ammonium fluoride gives the dicarbene **79**.



2-(4-Methylphenyl)benzothiazole (80IC762) and 2-benzylbenzothiazole (95ICA(239)125) can be cyclopalladated. In the latter case, cyclopalladation occurs upon reaction with palladium(II) acetate and gives the product **80**. With lithium chloride, sodium bromide, or sodium iodide, a series of three products of substitution of the acetate group **81** ( $X = \text{Cl}, \text{Br}, \text{I}$ ) results. Pyridine, 2- and 3-methylpyridine, 2,6- and 3,5-dimethylpyridine cause the transformation of the chelate complexes **81** ( $X = \text{Cl}, \text{Br}, \text{I}$ ) and formation of the mononuclear products **82** ( $R^2 = R^3 = R^4 = R^5 = R^6 = \text{H}, X = \text{Cl}, \text{Br}, \text{I}$ ;  $R^2 = \text{Me}, R^3 = R^4 = R^5 = R^6 = \text{H}, X = \text{Br}$ ;  $R^2 = R^4 = R^5 = R^6 = \text{H}, R^3 = \text{Me}, X = \text{Br}$ ;  $R^2 = R^6 = \text{Me}, R^3 = R^4 = R^5 = \text{H}, X = \text{Br}$ ;  $R^2 = R^4 = R^6 = \text{H}, R^3 = R^5 = \text{Me}, X = \text{Br}$ ). Thallium acetylacetonate when reacted with **81** ( $X = \text{Cl}, \text{Br}, \text{I}$ ) leads to the formation of the mononuclear product **83**.

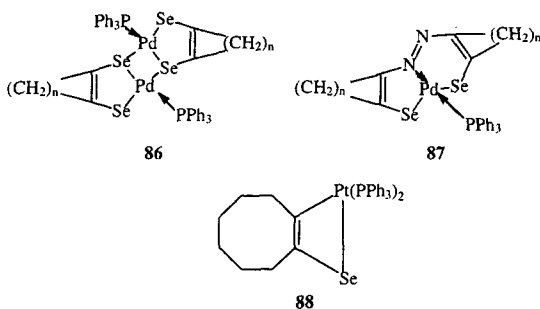


Lithium 2-thiolatobenzothiazole with  $[\text{Pd}(\mu\text{-Cl})(\eta^3\text{-C}_3\text{H}_5)_2]_2$  gives the dinuclear complex **84** (91JCS(D)255). The latter has the ligating potential and ability to form the trinuclear complex **85** on reaction with  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{Me}_2\text{CO})_2]\text{ClO}_4$ .



Tris(thiazol-2-yl)phosphine (L) and tris(benzothiazole-2-yl)phosphine (L) with  $[(\eta^4\text{-cod})\text{PtMe}_2]$  give the *cis*- $[\text{L}_2\text{PtMe}_2]$  complexes where the ligand is coordinated via its P donor center (73JOM(59)411, 76JA6521, 82JOC1489).

Reactions of cycloalkeno-1,2,3-selenadiazoles with  $[\text{Pd}(\text{PPh}_3)_4]$  in toluene under reflux present illustrations of denitrogenation reactions and yield the dinuclear diselenolenes **86** ( $n = 4, 5$ , and  $6$ ) (99JCS(D)791). At slightly lower temperatures, traces of the nitrogen-containing species **87** ( $n = 4, 5$ , and  $6$ ) are also present in the reaction mixture. A related type of the product, **88**, is formed upon interaction of cycloocteno-1,2,3-selenadiazole with  $[\text{Pt}(\text{PPh}_3)_4]$  (95JCR(S)64).



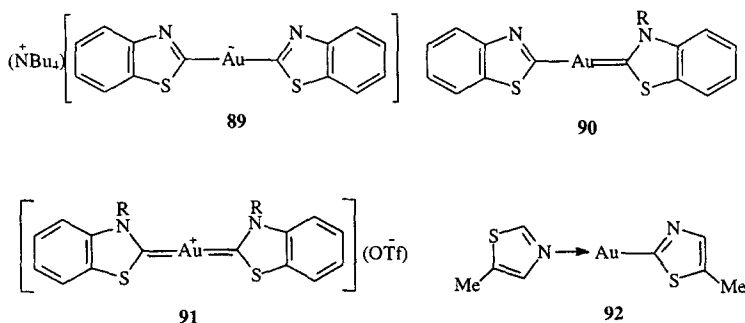
## IV. Late Transition Metal Complexes

### A. COPPER, SILVER AND GOLD

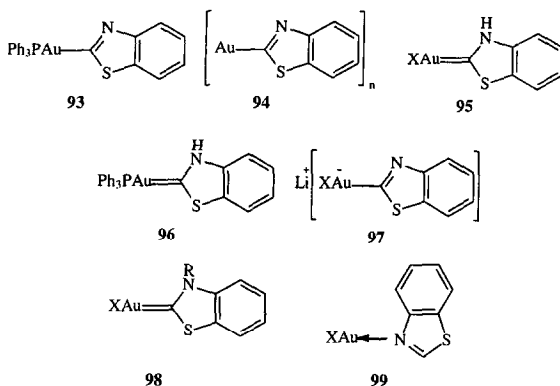
Derivatized thiazolyl lithium compounds react with copper(I) and silver(I) halides, and the products are subsequently protonated or alkylated



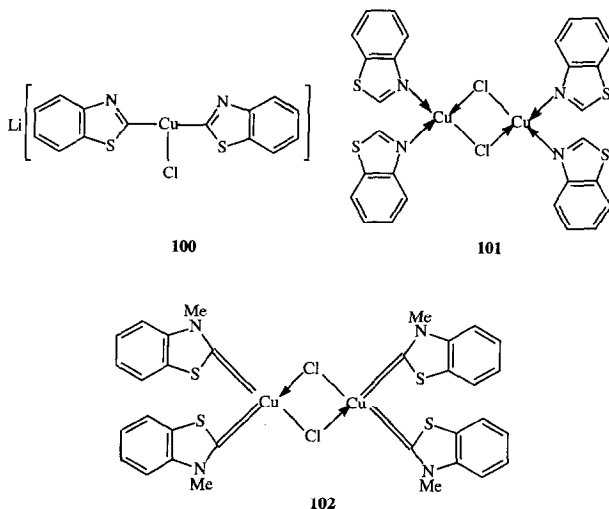
(94AGE672, 94JCS(D)2091). This serves as an efficient route to hydrothiazolylidene carbene derivatives of copper and silver. Lithium benzothiazolate or 4-methylthiazolate with  $[\text{ClAu}(\text{THT})]$  give the C-coordinated complexes isolated as tetra-*n*-butylammonium salts, e.g. **89** (90JCS(CC)1922, 93MI1, 01JOM(617)170). They can be further protonated or alkylated with triflic acid or methyl triflate to give the mixed ligand species **90** ( $\text{R} = \text{H}, \text{Me}$ ) or homoleptic bis-carbenes **91** ( $\text{R} = \text{H}, \text{Me}$ ). Interaction of 2-lithio-4-methylthiazolate with the methylating agent gives along with the analogue of **90** ( $\text{R} = \text{Me}$ ) complex **92**. The 4-methylthiazole analogue of **90** on further methylation gives the bis-carbene analogue of **91** ( $\text{R} = \text{Me}$ ).



Another precursor for the organogold carbene derivatives is  $[(\text{Ph}_3\text{P})\text{AuCl}]$ , which with lithiated benzothiazole and 4-methylthiazole gives C-coordinated complexes **93** (the benzothiazole derivative is given for illustration), which easily polymerizes to **94**, and on protonation by hydrochloric acid gives the carbene **95** ( $\text{X} = \text{Cl}$ ). However, if the reaction is run in the presence of triflic acid, the monocarbene **96** is formed straightforwardly. Methyl triflate gives the homoleptic dicarbene of the type **91** ( $\text{R} = \text{Me}$ ). Precursor  $[(\text{C}_6\text{F}_5)\text{Au}(\text{THT})]$  with lithium benzothiazolate and 4-methylthiazolate gives the anionic complexes **97** ( $\text{X} = \text{C}_6\text{F}_5$ ), which on methylation give the monocarbenes **98** ( $\text{X} = \text{C}_6\text{F}_5$ ,  $\text{R} = \text{Me}$ ) and on protonation with triflic acid a mixture of the monocarbene **98** ( $\text{X} = \text{C}_6\text{F}_5$ ,  $\text{R} = \text{H}$ ) and the N-coordinated products **99** (again the benzannulated ligand only is considered for the purposes of illustration). Gold(I) cyanide in these conditions behaves differently forming first the anionic C-coordinated species **97** ( $\text{X} = \text{CN}$ ), on alkylation the monocarbene **98** ( $\text{X} = \text{CN}$ ,  $\text{R} = \text{Me}$ ) but on protonation the homoleptic cationic dicarbenes **91**.



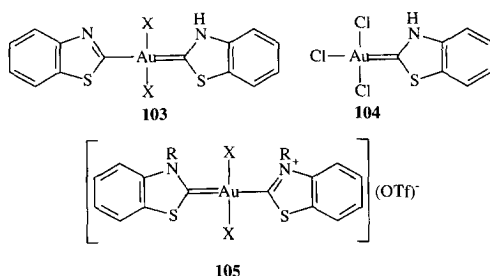
The same lithium salts with copper(I) chloride react through the stage of the anionic C-coordinated complexes **100**, which on protonation with hydrochloric acid give the corresponding 2,2'-bithiazoles, with triflic acid—the N-coordinated species **101**, and on methylation with methyl triflate they give carbenes of structure **102**.



Isothiazole forms the carbenes upon treatment of its lithium salt with  $[\text{C}_6\text{F}_5\text{Au}(\text{THT})]$  and methyl triflate while the C-coordinated complex formed before methylation was not isolated. When  $[\text{Ph}_3\text{PAuCl}]$  is used as the precursor, both C-coordinated complex and then carbene can be prepared (95JCS(D)2067).

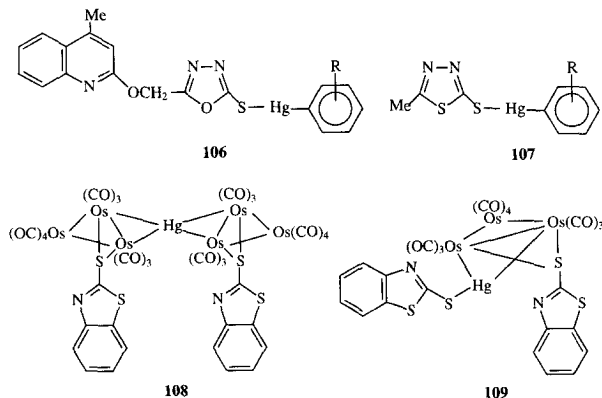
The reactivity pattern of some organogold derivatives is of interest. Thus, complex **90** oxidatively adds molecular chlorine, bromine, or iodine to yield the gold(III) product **103** (97JOM(544)91, 98JOM(552)69). The latter is

however not stable and undergoes reductive elimination of 2-chloro-(bromo-, or iodo-) benzothiazole to yield the monocarbene **95** ( $X = \text{Cl}, \text{Br}, \text{I}$ ). The chloro-derivative **95** ( $X = \text{Cl}$ ) may add molecular chlorine to yield the gold(III) monocarbene **104**. The bis-carbene complex **91** oxidatively adds molecular chlorine or bromine to yield the gold(III) product **105** ( $X = \text{Cl}, \text{Br}$ ). In the case of molecular iodine, the gold(III) product cannot be isolated but perhaps immediately as it is formed, it eliminates 2-iodobenzothiazole and forms the monocarbene of the type **95** ( $X = \text{I}$ ).

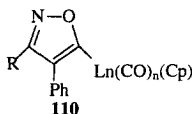


## B. MERCURY AND LANTHANIDES

2-Mercapto-5-[4'-methylquinolinyl-2-oxymethyl]-1,3,4-oxadiazole with aryl mercuric chlorides forms the S-coordinated species **106** ( $R = \text{H}, 4\text{-Me}, 4\text{-Cl}, 4\text{-Br}, 4\text{-OMe}$ ) (96POL2819). 2-Mercapto-5-methyl-1,3,4-thiadiazole reacts similarly to yield **107** ( $R = \text{H}, 4\text{-Me}, 4\text{-Cl}, 4\text{-Br}, 4\text{-OMe}$ ). A similar coordination mode is observed in the complexes obtained from 2-mercapto-benzothiazole with methylmercury hydroxide and phenylmercury acetate (85IC3435). The phenyl complex enters further interaction with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  and gives two principal products **108** and **109** (99JCS(DS)2497).



The C-coordination is realized in the lanthanide derivatives of isoxazole, **110** (89JOM(372)287)).



## V. Conclusions

1. The Group VI organometallic chemistry is mainly characterized by the occurrence of N- and C-coordination and carbene complex-formation, as well as by some unique cases of Se- (Te-) coordination, ring opening and deselenation. The Group VII organometallic chemistry is known for the carbene and chelate structures of the derivatized thiazoles.
2. Organoiron chemistry offers the C-coordination mode, carbene series, ring opening and detelluration. Organoruthenium and especially organoosmium species are sometimes peculiar: along with the classical cases of N-coordination and carbene formation, C,N- and S,N-cases can be traced.
3. In the rhodium and iridium complexes, the C-coordination, carbene function, and cyclometallated cases prevail. Benzothiazole-2-thione was studied extensively as a ligand and various situations of the exocyclic S-monodentate coordination as well as N,S-combinations in the di-, tri-, and tetranuclear species were discovered.
4. Complexes of the nickel subgroup include C-coordinated, carbene, ring-opened, and cyclopalladated cases, while N-coordination is scarce.
5. Organometallic complexes of copper, silver, and gold are ideal precursors for carbene complexes along with some C- and N-coordinated species. Their reactivity pattern, in particular in oxidative addition reactions, was the most comprehensively studied.

## REFERENCES

- |               |  |
|---------------|--|
| 68AGE950      | K. Öfele, <i>Angew. Chem., Int. Ed. Engl.</i> <b>7</b> , 950 (1968).                             |
| 69AGE916      | K. Öfele, <i>Angew. Chem., Int. Ed. Engl.</i> <b>9</b> , 916 (1969).                             |
| 71JOM(30)89   | W. Beck, J. C. Weis, and J. Wiczorek, <i>J. Organomet. Chem.</i> <b>30</b> , 89 (1971).          |
| 72JCS(P1)2165 | T. L. Gilchrist, P. G. Mente, and C. W. Rees, <i>J. Chem. Soc., Perkin Trans. 1</i> 2165 (1972). |
| 73JA2501      | G. N. Schrauzer and H. Kisch, <i>J. Am. Chem. Soc.</i> <b>95</b> , 2501 (1973).                  |

- 73JOM(50)C54 P. J. Fraser, W. R. Roper, and F. G. A. Stone, *J. Organomet. Chem.* **50**, C54 (1973).
- 73JOM(59)411 H. C. Clark and L. E. Manzer, *J. Organomet. Chem.* **59**, 411 (1973).
- 74IC225 R. Alper and A. S. K. Chan, *Inorg. Chem.* **13**, 225 (1974).
- 74JCS(D)102 P. J. Fraser, W. R. Roper, and F. G. A. Stone, *J. Chem. Soc., Dalton Trans.* 102 (1974).
- 74JCS(D)760 P. J. Fraser, W. R. Roper, and F. G. A. Stone, *J. Chem. Soc., Dalton Trans.* 760 (1974).
- 75ICA(12)127 K. H. Panell, C. C. X. Lee, C. Parkanyi, and R. Redfearn, *Inorg. Chim. Acta* **12**, 127 (1975).
- 75JCS(D)939 M. Green, F. G. A. Stone, and M. Underhill, *J. Chem. Soc., Dalton Trans.* 939 (1975).
- 75JLAC533 B. Schroder, U. Schollkopf, E. Blume, and J. Hoppe, *J. Liebigs Ann. Chem.* 533 (1975).
- 76JA6521 J. X. McDermott, J. F. White, and G. M. Whitesides, *J. Am. Chem. Soc.* **98**, 6521 (1976).
- 76JCS(CC)743 C. C. Ashworth, N. A. Bailey, M. Johnson, J. A. McCleverty, N. Morrison, and B. Tabbiner, *J. Chem. Soc., Chem. Commun.* 743 (1976).
- 76TMC186 S. Jeannin, Y. Jeannin, and G. Lavigne, *Transition Met. Chem. (Weinheim, Ger.)* **1**, 186 (1976).
- 76TMC192 S. Jeannin, Y. Jeannin, and G. Lavigne, *Transition Met. Chem. (Weinheim, Ger.)* **1**, 192 (1976).
- 76TMC195 S. Jeannin, Y. Jeannin, and G. Lavigne, *Transition Met. Chem. (Weinheim, Ger.)* **1**, 195 (1976).
- 78IC2103 S. Jeannin, Y. Jeannin, and G. Lavigne, *Inorg. Chem.* **17**, 2103 (1978).
- 78TL5 E. J. Corey and D. Boger, *Tetrahedron Lett.* 5 (1978).
- 78TL9 E. J. Corey and D. Boger, *Tetrahedron Lett.* 9 (1978).
- 78TL13 E. J. Corey and D. Boger, *Tetrahedron Lett.* 13 (1978).
- 79JOC2042 P. A. Jacobi, S. Ueng, and D. Carr, *J. Org. Chem.* **44**, 2042 (1979).
- 80AGE632 K. H. Pannell, A. J. Mayr, R. Hoggard, and R. Petterson, *Angew. Chem., Int. Ed. Engl.* **19**, 632 (1980).
- 80IC762 M. R. Churchill, H. I. Wasserman, and G. J. Young, *Inorg. Chem.* **19**, 762 (1980).
- 81IC2778 G. Boxhoorn, D. J. Stufkens, P. J. F. M. C. Wijk, and A. M. F. Hezemans, *Inorg. Chem.* **20**, 2778 (1981).
- 81ZN(B)172 V. Bitzel and R. Boese, *Z. Naturforsch.* **B36**, 172 (1981).
- 82AGE700 W. Kaim and V. Kasack, *Angew. Chem., Int. Ed. Engl.* **21**, 700 (1982).
- 82JOC1489 S. S. Moore and G. M. Whitesides, *J. Org. Chem.* **47**, 1489 (1982).
- 83CB230 K. H. Pannell, A. J. Mayr, R. Hoggard, J. S. McKennis, and J. C. Dawson, *Chem. Ber.* **116**, 230 (1983).
- 83OM560 K. H. Pannell, A. J. Mayr, and D. Van Derveer, *Organometallics* **2**, 560 (1983).
- 85IC3435 J. Bravo, J. S. Casas, M. V. Castano, M. Gayoso, Y. P. Mascarenhas, A. Sanchez, C. O. P. Santos, and J. Sordo, *Inorg. Chem.* **24**, 3435 (1985).
- 85OM275 H. G. Raubenheimer, G. J. Kruger, A. A. Lombaard, L. Linford, and J. C. Viljoen, *Organometallics* **4**, 275 (1985).
- 85TL5477 A. Dondoni, M. Fogagnolo, A. Medici, and P. Pedrini, *Tetrahedron Lett.* 5477 (1985).

- 85TMC413 R. Rossi, A. Duatti, L. Magon, A. Marchi, A. Medici, M. Fogagnolo, U. Casellato, and R. Graziani, *Transition Met. Chem. (Weinheim, Ger.)* **10**, 413 (1985).
- 86JCS(CC)1737 M. A. Ciriano, L. A. Oro, J. J. Perez-Torrente, A. Tiripicchio, and M. Tiripicchio-Camellini, *J. Chem. Soc., Chem. Commun.* 1737 (1986).
- 86NJC75 L. A. Oro, M. A. Ciriano, F. Viguri, A. Tiripicchio, M. Tiripicchio-Camellini, and F. J. Lahoz, *New J. Chem.* **10**, 75 (1986).
- 87AGE444 M. A. Ciriano, L. A. Oro, A. Tiripicchio, and M. Tiripicchio-Camellini, *Angew. Chem., Int. Ed. Engl.* **26**, 444 (1987).
- 87JCS(CC)63 A. J. Banister, M. I. Hansford, and Z. V. Hauptman, *J. Chem. Soc., Chem. Commun.* 63 (1987).
- 87JCS(D)2299 R. Rossi, A. Marchi, A. Duatti, L. Magon, U. Casellato, and R. Graziani, *J. Chem. Soc., Dalton Trans.* 2299 (1987).
- 88AGE402 M. A. Ciriano, S. Sebastian, L. A. Oro, A. Tiripicchio, M. Tiripicchio-Camellini, and F. J. Lahoz, *Angew. Chem., Int. Ed. Engl.* **27**, 402 (1988).
- 88BCSJ3637 H. Chikashita, M. Ishibaba, K. Ori, and K. Itoh, *Bull. Chem. Soc. Jpn.* **61**, 3637 (1988).
- 88ICA(151)209 M. M. Muir, M. E. Cadiz, and A. Baez, *Inorg. Chim. Acta* **151**, 209 (1988).
- 88JCS(D)899 R. Rossi, A. Martchi, A. Duatti, L. Magon, U. Casellato, and R. Graziani, *J. Chem. Soc., Dalton Trans.* 899 (1988).
- 88JOM(338)C31 M. F. M. Al-Dulaymmi, P. B. Hitchcock, and R. L. Richards, *J. Organomet. Chem.* **338**, C31 (1988).
- 88OM1939 B. J. Rappoli, T. S. Janik, M. R. Churchill, J. S. Thompson, and J. D. Atwood, *Organometallics* **7**, 1939 (1988).
- 88POL219 A. O. Baghlaf, M. Ishaq, S. A. Rahman, A. B. Al-Tahir, A. Zaidan, and R. A. Kabli, *Polyhedron* **7**, 219 (1988).
- 88ZN(B)328 W. Weigand, U. Nagel, and W. Beck, *Z. Naturforsch.* **B43**, 328 (1988).
- 89ICA(160)23 R. Rossi, A. Marchi, L. Magon, A. Duatti, U. Caselatto, and R. Graziani, *Inorg. Chim. Acta* **160**, 23 (1989).
- 89JCS(D)25 M. A. Ciriano, F. Viguri, J. J. Perez-Torrente, L. A. Oro, A. Tiripicchio, and M. Tiripicchio-Camellini, *J. Chem. Soc., Dalton Trans.* 25 (1989).
- 89JCS(D)1705 A. J. Banister, M. I. Hansford, Z. V. Hauptman, S. T. Wait, and W. Clegg, *J. Chem. Soc., Dalton Trans.* 1705 (1989).
- 89JCS(D)2229 A. J. Banister, I. B. Gorrell, W. Clegg, and K. A. Jorgensen, *J. Chem. Soc., Dalton Trans.* 2229 (1989).
- 89JOM(372)287 V. N. Kalinin, T. V. Rozantseva, P. V. Petrovskii, A. S. Batsanov, and Y. T. Struchkov, *J. Organomet. Chem.* **372**, 287 (1989).
- 89JOM(377)151 M. Herberhold and A. F. Hill, *J. Organomet. Chem.* **377**, 151 (1989).
- 89OM800 C. P. Morley, *Organometallics* **8**, 800 (1989).
- 89OM2961 A. J. Mayr, K. H. Pannell, B. Carrasco-Flores, and F. Cervantes-Lee, *Organometallics* **8**, 2961 (1989).
- 90ICA(168)47 M. M. Muir, G. M. Gomez, M. E. Cadiz, and J. A. Muir, *Inorg. Chim. Acta* **168**, 47 (1990).
- 90JCS(CC)1922 H. G. Raubenheimer, F. Scott, M. Roos, and R. Otte, *J. Chem. Soc., Chem. Commun.* 1922 (1990).

- 90JCS(D)1493 M. A. Ciriano, J. J. Perez-Torrente, F. Viguri, F. J. Lahoz, L. A. Oro, A. Tiripicchio, and M. Tiripicchio-Camellini, *J. Chem. Soc., Dalton Trans.* 1493 (1990).
- 90JCS(D)1737 N. W. Alcock, A. F. Hill, and M. S. Roe, *J. Chem. Soc., Dalton Trans.* 1737 (1990).
- 90JCS(D)2793 A. J. Banister, M. I. Hansford, Z. V. Hauptman, A. W. Luke, S. T. Wait, W. Clegg, and K. A. Jorgensen, *J. Chem. Soc., Dalton Trans.* 2793 (1990).
- 90OM12 K. A. Bernard, M. R. Churchill, T. S. Janik, and J. D. Atwood, *Organometallics* **9**, 12 (1990).
- 91AX(C)1539 M. Rong, M. M. Muir, M. E. Cadiz, and J. A. Muir, *Acta Crystallogr.* **C47**, 1539 (1991).
- 91JCS(D)255 M. A. Ciriano, J. J. Perez-Torrente, L. A. Oro, A. Tiripicchio, and M. Tiripicchio-Camellini, *J. Chem. Soc., Dalton Trans.* 255 (1991).
- 91JCS(D)1105 A. J. Banister, I. B. Gorrell, W. Clegg, and K. A. Jorgensen, *J. Chem. Soc., Dalton Trans.* 1105 (1991).
- 91JCS(D)1563 J. G. Toerien and P. H. van Rooyen, *J. Chem. Soc., Dalton Trans.* 1563 (1991).
- 91JOC449 J. C. Hodges, W. C. Patt, and C. J. Connolly, *J. Org. Chem.* **56**, 449 (1991).
- 91JOC3058 S. E. Whitney and B. Rickborn, *J. Org. Chem.* **56**, 3058 (1991).
- 91JOM(405)309 A. J. Mayr, B. Carrasco-Flores, F. Cervantes-Lee, K. H. Pannell, L. Parkanyi, and K. Raghu Veer, *J. Organomet. Chem.* **405**, 309 (1991).
- 91OM3903 C. J. Harris and A. F. Hill, *Organometallics* **10**, 3903 (1991).
- 91OM3906 J. S. Thompson, S. L. Randall, and J. D. Atwood, *Organometallics* **10**, 3906 (1991).
- 92HC87 R. J. Dorrity, A. Lavery, J. F. Malone, C. P. Morley, and R. R. Vaughan, *Heteroat. Chem.* **3**, 87 (1982).
- 92IC634 M. Van Beusichem and N. Farrell, *Inorg. Chem.* **31**, 634 (1992).
- 92IC969 M. A. Ciriano, J. J. Perez-Torrente, F. J. Lahoz, and L. A. Oro, *Inorg. Chem.* **31**, 969 (1992).
- 92ICA(191)138 M. M. Muir, O. Cox, L. A. Rivera, M. E. Cadiz, and E. Medina, *Inorg. Chim. Acta* **191**, 138 (1991).
- 92JA5467 A. J. Mayr, B. Carrasco-Flores, L. Parkanyi, and K. H. Pannell, *J. Am. Chem. Soc.* **114**, 5467 (1992).
- 92JCS(D)241 M. F. M. Al-Dulaymmi, A. Hills, P. B. Hitchcock, D. L. Hughes, and R. L. Richards, *J. Chem. Soc., Dalton Trans.* 241 (1992).
- 92JCS(D)1009 H. G. Raubenheimer, F. Scott, S. Cronje, P. H. van Rooyen, and K. Psotta, *J. Chem. Soc., Dalton Trans.* 1009 (1992).
- 92JOM(438)209 C. J. Harris and A. F. Hill, *J. Organomet. Chem.* **438**, 209 (1992).
- 92MI1 A. W. Cordes, R. C. Haddon, and R. T. Oakley, in "The Chemistry of Inorganic Ring Systems", (R. Steudel, ed.), p. 295 (1992) Elsevier, Amsterdam.
- 92MI2 J. M. Rawson and A. J. Banister, in "The Chemistry of Inorganic Ring Systems", (R. Steudel, ed.), pp. 323 (1992) Elsevier, Amsterdam.
- 93AHC47 I. D. Sadkov and V. I. Minkin, *Adv. Heterocycl. Chem.* **58**, 47 (1993).
- 93JCS(D)703 C. P. Morley and R. R. Vaughan, *J. Chem. Soc., Dalton Trans.* 703 (1993).

- 93JOM(444)219 C. P. Morley and R. R. Vaughan, *J. Organomet. Chem.* **444**, 219 (1993).
- 93JOM(455)225 M. A. Ciriano, J. J. Perez-Torrente, F. J. Lahoz, and L. A. Oro, *J. Organomet. Chem.* **455**, 225 (1993).
- 93JOM(459)271 D. Seyferth, L. L. Anderson, and W. M. Davis, *J. Organomet. Chem.* **459**, 271 (1993).
- 93MII H. G. Raubenheimer, S. Cronje, R. Otte, W. van Zyl, I. Taljaard, and P. Olivier, in "Transition Metal Carbyne Complexes", (F. R. Kreissl, ed.) p. 169. (1993) Kluwer, Dordrecht.
- 94AGE672 H. G. Raubenheimer, S. Cronje, P. H. van Rooyen, P. J. Olivier, and J. G. Toerien, *Angew. Chem., Int. Ed. Engl.* **33**, 672 (1994).
- 94JA5180 V. C. M. Smith, R. T. Aplin, J. M. Brown, M. B. Hursthouse, A. I. Karaulov, K. M. A. Malik, and N. A. Cooley, *J. Am. Chem. Soc.* **116**, 5180 (1994).
- 94JCS(D)2091 H. G. Raubenheimer, F. Scott, G. J. Kruger, J. G. Toerien, R. Otte, W. van Zyl, I. Taljaard, P. J. Olivier, and L. Linford, *J. Chem. Soc., Dalton Trans.* 2091 (1994).
- 94JOM(469)C31 M. A. Ciriano, M. Lanfranchi, L. A. Oro, J. J. Perez-Torrente, A. Tiripicchio, and M. Tiripicchio-Camellini, *J. Organomet. Chem.* **468**, C31 (1994).
- 94JOM(479)C12 J. G. Toerien, M. Desmet, G. J. Kruger, and H. G. Raubenheimer, *J. Organomet. Chem.* **479**, C12 (1994).
- 94PSS449 V. Klassen, K. Preuss, K. H. Moock, and R. T. Boere, *Phosphorus Sulfur Silicon* **93-94**, 449 (1994).
- 95AHC137 A. J. Banister, J. M. Rawson, and I. Lavender, *Adv. Heterocycl. Chem.* **62**, 137 (1995).
- 95ICA(239)125 Y. Fuchita, K. Yoshinaga, H. Kusaba, M. Mori, K. Hirtaki, and K. Takehara, *Inorg. Chim. Acta* **239**, 125 (1995).
- 95JCR(S)30 H. G. Raubenheimer and M. Desmet, *J. Chem. Res. (S)* 30 (1995).
- 95JCR(S)64 P. K. Khanna and C. P. Morley, *J. Chem. Res. (S)* 64 (1995).
- 95JCS(D)2067 H. G. Raubenheimer, M. Desmet, and G. J. Kruger, *J. Chem. Soc., Dalton Trans.* 2067 (1995).
- 95OM4764 M. A. Ciriano, J. A. Lopez, L. A. Oro, and J. J. Perez-Torrente, *Organometallics* **14**, 4764 (1995).
- 95SRIMOC115 P. Alvarez-Boo, E. Freijanes, E. G. Martinez, J. S. Casas, and J. Sordo, *Synth. React. Inorg. Met.-Org. Chem.* **25**, 115 (1995).
- 96IC4264 J. Campbell, D. Klapstein, P. F. Bernath, W. M. Davis, R. T. Oakley, and J. D. Goddard, *Inorg. Chem.* **35**, 4264 (1996).
- 96JCS(D)1731 K. A. Azam, R. Dilshad, S. E. Kabir, K. Khatoon, L. Nessa, M. N. Rahman, E. Rosenberg, M. B. Hursthouse, K. A. M. Malik, A. J. Deeming, *J. Chem. Soc., Dalton Trans.* 1731 (1996).
- 96JCS(D)3231 R. Kunz, P. Le Grel, and W. P. Fehlhammer, *J. Chem. Soc., Dalton Trans.* 3231 (1996).
- 96KK376 A. D. Garnovskii, I. D. Sadekov, A. S. Antsyshkina, I. S. Vasilchenko, A. I. Uraev, G. G. Sadikov, A. A. Maksimenko, G. S. Borodkin, and V. I. Minkin, *Koord. Khim.* **22**, 376 (1996).
- 96KK512 A. D. Garnovskii, A. I. Uraev, A. S. Antsyshkina, I. D. Sadekov, and V. I. Minkin, *Koord. Khim.* **22**, 512 (1996).
- 96POL2819 M. Kidwai and Y. Goel, *Polyhedron* **15**, 2819 (1996).



- 96ZNK1297 A. D. Garnovskii, A. S. Antsyshkina, I. S. Vasilchenko, O. Y. Korshunov, G. G. Sadikov, A. A. Maksimenko, and I. D. Sadekov, *Zh. Neorg. Khim.* **41**, 1297 (1996).
- 97AGE1709 G. Maier, J. Endres, and H. P. Reisenauer, *Angew. Chem., Int. Ed. Engl.* **36**, 1709 (1997).
- 97CB1213 C. Hill, F. Bosold, K. Harms, M. Marsch, and G. Boche, *Chem. Ber.* **130**, 1213 (1997).
- 97JOM(541)51 U. Kernbach, T. Lugger, F. E. Hahn, and W. P. Fehlhammer, *J. Organomet. Chem.* **541**, 51 (1997).
- 97JOM(544)91 H. G. Raubenheimer, P. J. Olivier, L. Lindeque, M. Desmet, J. Hrusak, and G. J. Kruger, *J. Organomet. Chem.* **544**, 91 (1997).
- 97OM3194 K. Badyal, W. R. McWinnie, T. A. Hamor, and H. Chen, *Organometallics* **16**, 3194 (1997).
- 97ZN(B)1199 B. Schreiner, M. Prem, W. Bauer, K. Polborn, and W. Beck, *Z. Naturforsch.* **B52**, 1199 (1997).
- 98JCS(D)3501 A. F. Hill and J. D. E. T. Wilton-Fly, *J. Chem. Soc., Dalton Trans.* 3501 (1998).
- 98JOM(552)69 P. Kuhlkamp, H. G. Raubenheimer, J. S. Field, and M. Desmet, *J. Organomet. Chem.* **552**, 69 (1998).
- 98OM513 K. H. Yih, S. C. Yeh, Y. C. Lin, G. H. Lee, and Y. Wang, *Organometallics* **17**, 513 (1998).
- 99AHC1 A. D. Garnovskii and A. P. Sadimenko, *Adv. Heterocycl. Chem.* **72**, 1 (1999).
- 99JCS(D)791 S. Ford, P. K. Khanna, C. P. Morley, and M. Di Vaira, *J. Chem. Soc., Dalton Trans.* 791 (1999).
- 99JCS(DS)2497 F. S. Kong and W. T. Wong, *J. Chem. Soc., Dalton Trans.* 2497 (1999).
- 99JOM(575)51 S. M. Kuang, Z. Z. Zhang, F. Xue, and T. C. W. Mak, *J. Organomet. Chem.* **575**, 51 (1999).
- 99JOM(590)158 H. G. Raubenheimer, Y. Stander, E. K. Marais, C. Thompson, G. J. Kruger, S. Cronje, and M. Deetlefs, *J. Organomet. Chem.* **590**, 158 (1999).
- 00EJ129 B. Cetinkaya, I. Ozdemir, C. Bruneau, and P. H. Dixneuf, *Eur. J. Inorg. Chem.* 29 (2000).
- 01AHC(78)1 A. P. Sadimenko, *Adv. Heterocycl. Chem.* **78**, 1 (2001).
- 01AHC(79)115 A. P. Sadimenko, *Adv. Heterocycl. Chem.* **79**, 115 (2001).
- 01AHC(80)157 A. P. Sadimenko, *Adv. Heterocycl. Chem.* **80**, 157 (2001).
- 01AHC(81)167 A. P. Sadimenko, *Adv. Heterocycl. Chem.* **81**, 167 (2001).
- 01IC1704 S. Lamansky, P. Djurovich, D. Murphy, F. Abdel-Razzaq, I. Tsyba, M. Bortz, B. Mui, R. Bau, and M. E. Thompson, *Inorg. Chem.* **40**, 1704 (2001).
- 01ICA(314)91 X. Chen, F. J. Femia, J. W. Babich, and J. Zubieta, *Inorg. Chim. Acta* **314**, 91 (2001).
- 01JOM(617)170 H. G. Raubenheimer and S. Cronje, *J. Organomet. Chem.* **617–618**, 170 (2001).
- 02AHC(83)117 A. P. Sadimenko, *Adv. Heterocycl. Chem.* **83**, 117 (2002).

# Recent Development in the Chemistry of Pyrido-oxazines, Pyrido-thiazines, Pyrido-diazines and Their Benzologs: Part 1

ISTVÁN HERMECZ

*Chinoin Pharmaceutical and Chemical Works, Ltd., Research Center,  
Budapest, Hungary*

I. Introduction .....	222
II. Pyrido[1,2- <i>b</i> ][1,2]oxazines and Their Benzologs .....	226
A. Structure .....	226
1. NMR Spectroscopy .....	226
2. X-ray Investigation .....	226
B. Reactivity .....	226
1. Ring Opening .....	226
2. Hydrogenation, Reduction .....	227
3. Reactivity of Rings .....	228
4. Reactivity of Substituents Attached to Ring Carbon Atoms .....	229
C. Synthesis .....	219
1. Miscellaneous .....	229
D. Applications and Important Compounds .....	231
III. Pyrido[1,2- <i>b</i> ][1,2]benzothiazines .....	231
A. Structure .....	231
1. X-ray Investigation .....	231
B. Reactivity .....	232
1. Hydrogenation .....	232
2. Reactivity of Substituents Attached to Ring Carbon Atoms .....	232
C. Synthesis .....	232
1. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )] .....	232
IV. Pyrido[1,2- <i>b</i> ]pyridazines and Their Benzo Derivatives .....	234
A. Structure .....	234
1. Theoretical Calculation .....	234
2. X-ray Investigations .....	235
B. Reactivity .....	236
1. Ring Opening .....	236
2. Oxidation .....	236
3. Reactivity of Substituents Attached to Ring Carbon Atoms .....	236
4. Rearrangement .....	237
C. Synthesis .....	237
1. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )] .....	237

2. By Fragments of Two Bonds from [4 + 2] Atom Fragments . . . . .	237
3. Ring Transformation . . . . .	239
V. Pyrido[1,2- <i>c</i> ][1,3]oxazines and Their Benzologs . . . . .	240
A. Structure . . . . .	240
1. Infrared Spectroscopy . . . . .	240
2. NMR Spectroscopy . . . . .	240
B. Reactivity . . . . .	240
1. Ring Opening . . . . .	240
2. Reactivity of Ring Carbon Atoms . . . . .	241
3. Reactivity of Substituents Attached to Ring Carbon Atoms . . . . .	242
C. Synthesis . . . . .	243
1. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0( $\beta$ )] . . . . .	243
2. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )] . . . . .	244
3. By Formation of Two Bonds from [5 + 1] Atom Fragments . . . . .	244
4. By Formation of Two Bonds from [4 + 2] Atom Fragments . . . . .	246
5. Miscellaneous . . . . .	246
D. Application and Important Compounds . . . . .	247
VI. Pyrido[1,2- <i>c</i> ]pyrimidines and Their Benzologs . . . . .	247
A. Structure . . . . .	247
1. Thermodynamic Aspects . . . . .	247
2. Theoretical Calculations . . . . .	247
3. NMR Spectroscopy . . . . .	248
4. Mass Spectrometry . . . . .	248
5. X-ray Investigations . . . . .	249
B. Reactivity . . . . .	249
1. Ring Opening . . . . .	249
2. Reduction and Oxidation . . . . .	250
3. Reactivity of Ring Nitrogen . . . . .	251
4. Reactivity of Substituents Attached to Ring Nitrogen Atom . . . . .	252
5. Reactivity of Ring Carbon Atoms . . . . .	253
6. Reactivity of Substituents Attached to Ring Carbon Atoms . . . . .	253
C. Synthesis . . . . .	257
1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6 + 0( $\alpha$ )] . . . . .	257
2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0( $\beta$ )] . . . . .	257
3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )] . . . . .	258
4. By Formation of Two Bonds from [5 + 1] Atom Fragments . . . . .	259
5. By Formation of Two Bonds from [4 + 2] Atom Fragments . . . . .	561
6. Ring Transformation . . . . .	561
7. Miscellaneous . . . . .	561
D. Applications and Important Compounds . . . . .	262
VII. Pyrido[2,1- <i>c</i> ][1,4]oxazines and Their Benzo Derivatives . . . . .	263
A. Structure . . . . .	263
1. Thermodynamic Aspects . . . . .	263
2. Theoretical Calculations . . . . .	267
3. UV, Fluorescence and IR Spectroscopy . . . . .	268

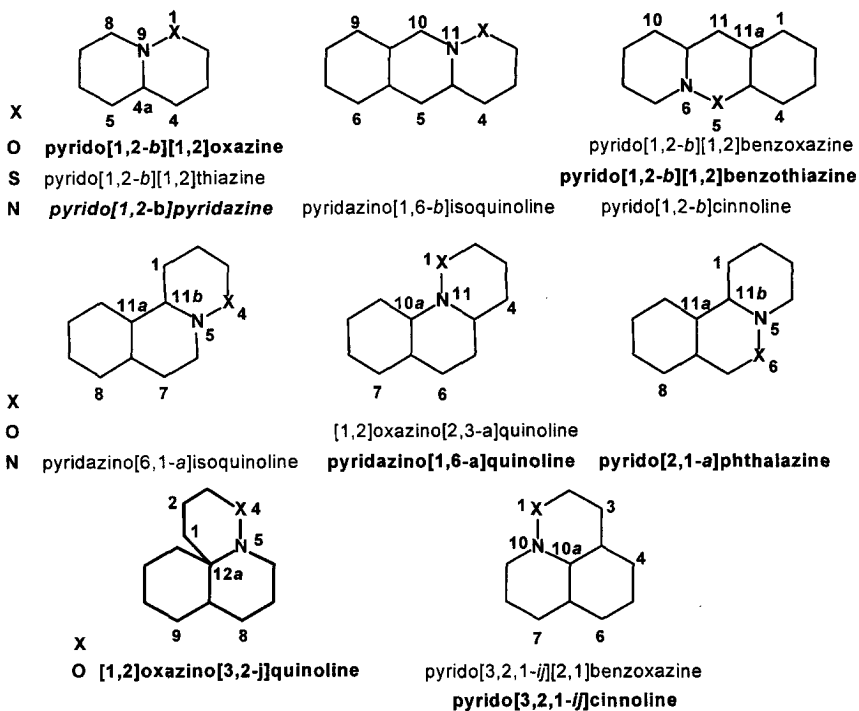
4. NMR Spectroscopy	268
5. Mass Spectrometry	268
6. X-ray Investigation	269
B. Reactivity	269
1. Ring Opening	269
2. Reduction, Hydrogenation	272
3. Oxidation	273
4. Reactivity of Ring Carbon Atoms	274
5. Reaction of Substituents Attached to Ring Carbon Atoms	276
6. Ring Transformation	278
7. Miscellaneous	279
C. Synthesis	279
1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen	
Atom [6 + 0( $\alpha$ )]	279
2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen	
Atom [6 + 0( $\beta$ )]	280
3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen	
Atom [6 + 0( $\gamma$ )]	281
4. By Formation of Two Bonds from [4 + 2] Atom Fragments	285
5. By Formation of Two Bonds from [3 + 3] Atom Fragments	286
6. Ring Transformations	286
7. Miscellaneous	287
D. Applications and Important Compounds	290
VIII. Pyrido[2,1- <i>c</i> ][1,4]thiazines and Their Benzologs	292
A. Structure	292
1. Thermodynamic Aspects	292
2. Theoretical Calculations	292
3. Mass Spectroscopy	293
B. Reactivity	293
1. Reduction	293
2. Oxidation	293
3. Reactivity of Ring Carbon Atoms	293
4. Reactivity of Substituent Attached to Ring Carbon Atoms	294
5. Miscellaneous	295
C. Synthesis	295
1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen	
Atom [6 + 0( $\alpha$ )]	295
2. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen	
Atom [6 + 0( $\gamma$ )]	296
3. By Formation of Two Bonds from [5 + 1] Atom Fragments	296
4. By Formation of Two Bonds from [4 + 2] Atom Fragments	296
5. By Formation of Two Bonds from [3 + 3] Atom Fragments	297
6. Ring Transformation	297
D. Applications and Important Compounds	298
IX. Pyrido[1,2- <i>a</i> ]pyrazines and Their Benzologs	298
A. Structure	298
1. Thermodynamic Aspects	298
2. Theoretical Calculations	300
3. IR Spectroscopy	300
4. $^1\text{H}$ NMR Spectroscopy	300

5. X-ray Investigation	301
B. Reactivity	301
1. Reduction, Hydrogenation	301
2. Oxidation	304
3. Reactivity of Ring Nitrogen Atom	305
4. Reactivity of Substituents Attached to Ring Nitrogen Atom	307
5. Reactivity of Ring Carbon Atoms	308
6. Reactivity of Substituents Attached to Ring Carbon Atoms	310
7. Ring Transformations	315
8. Miscellaneous	316
C. Synthesis	316
1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6 + 0( $\alpha$ )]	316
2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0( $\beta$ )]	318
3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )]	318
4. By Formation of Two Bonds from [5 + 1] Atom Fragments	320
5. By Formation of Two Bonds from [4 + 2] Atom Fragments	321
6. By Formation of Two Bonds from [3 + 3] Atom Fragments	321
7. Ring Transformation	321
8. Miscellaneous	322
D. Applications and Important Compounds	323
E. References	325

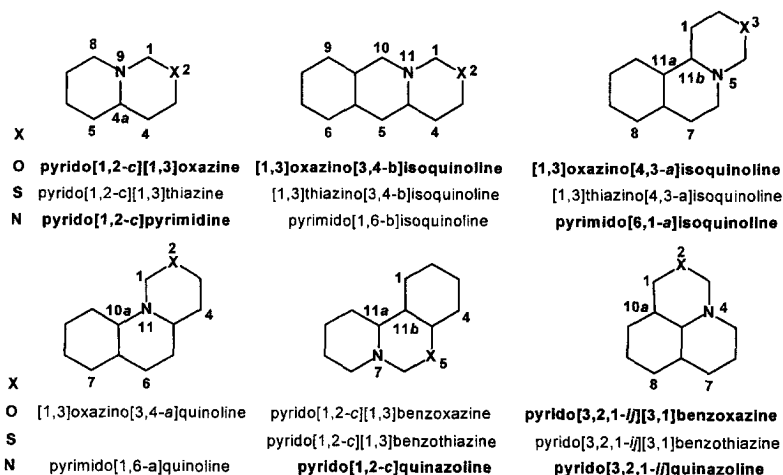
## I. Introduction

This review surveys the recent development in the chemistry of pyrido-oxazines, pyrido-thiazines, pyrido-diazines and their benzologs in two parts. The first part covers the ring systems depicted in Schemes 1–3. The chemistry of the bicyclic 6-6 system containing one ring junction nitrogen and one extra heteroatom and their benzologs was reviewed in 1996 (96CHCII(8)563), except for the chemistry of pyrido[1,2-*b*][1,2]benzothiazines, which has not been summarized until now. The early articles on pyrido[1,2-*b*][1,2]oxazine (61HC(15-2)1211), pyrido[1,2-*c*][1,3]oxazines (61HC(15-2)1201), pyrido[1,2-*c*]pyrimidines (61HC(15-2)1203), pyrimido[6,1-*a*]isoquinolines (61HC(15-2)1207), pyrido[2,1-*c*][1,4]thiazines (61HC(15-2)1182), pyrido[1,2-*a*]pyrazines (61HC(15-2)1188), pyrido[1,2-*a*]quinoxalines (61HC(15-2)1191), pyrazino[1,2-*a*]quinolines (61HC(15-2)1192), pyrido[1,2,3-*de*]-1,4-benzoxazines (61HC(15-2)1180), pyrido[1,2,3-*de*]quinoxalines (61HC(15-2)1193) were covered by Mosby's book in 1961.

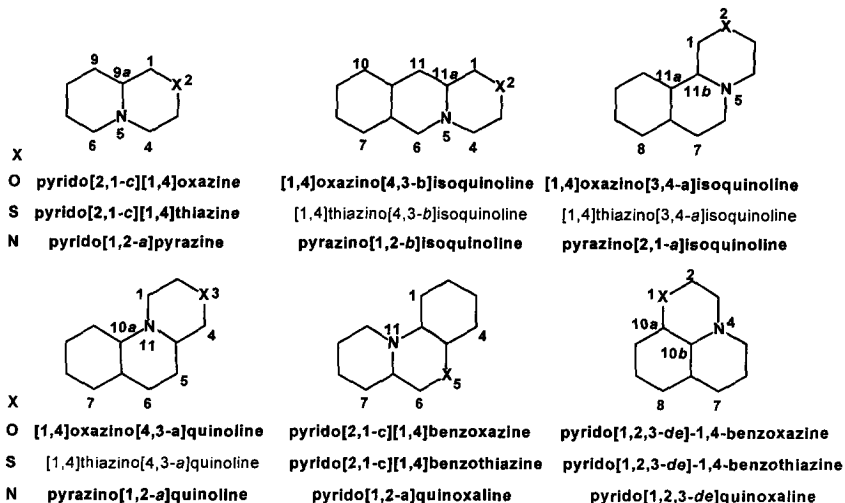
Furthermore, the chemistry of pyrido[1,2-*b*][1,2]oxazines, pyrido[1,2-*b*][1,2]thiazines, pyrido[1,2-*b*]pyridazines, and their benzologs (Scheme 1) was treated in 1998 (98AHC(69)89), that of pyrido[1,2-*c*][1,3]oxazines,



Scheme 1



Scheme 2



Scheme 3

pyrido[1,2-c][1,3]thiazines, pyrido[1,2-c]pyrimidines and their benzologs (Scheme 2) was reviewed in 1998 (98AHC(70)1). A review was published in 1986 including pyrido[1,2-c]quinazolines and pyrido[1,2-a]quinazolines (86AHC(39)281). The chemistry of pyrido[2,1-c][1,4]oxazines, pyrido[2,1-c][1,4]thiazines, pyrido[1,2-a]pyrazines and their benzologs (Scheme 3) was treated in 1998 (98AHC(71)145).

This article covers the primary chemical literature of bicyclic 6-6 system containing one ring junction nitrogen and one extra heteroatom and their benzologs contained in *Chemical Abstract* Chemical Substance Indexes up to Volume 135 from Volume 125 for pyrido[1,2-b][1,2]oxazines, pyrido[1,2-b]thiazines, pyrido[1,2-b]pyridazines, pyrido[1,2-c][1,3]oxazines, pyrido[1,2-c][1,3]thiazines, pyrido[1,2-c]pyrimidines and their benzologs; from Volume 126 for pyrido[2,1-c][1,4]oxazines, pyrido[2,1-c][1,4]thiazines, pyrido[1,2-a]pyrazines and their benzologs. In Schemes 1–3 the names of ring systems are in bold which were treated in papers and patents in the above indicated period.

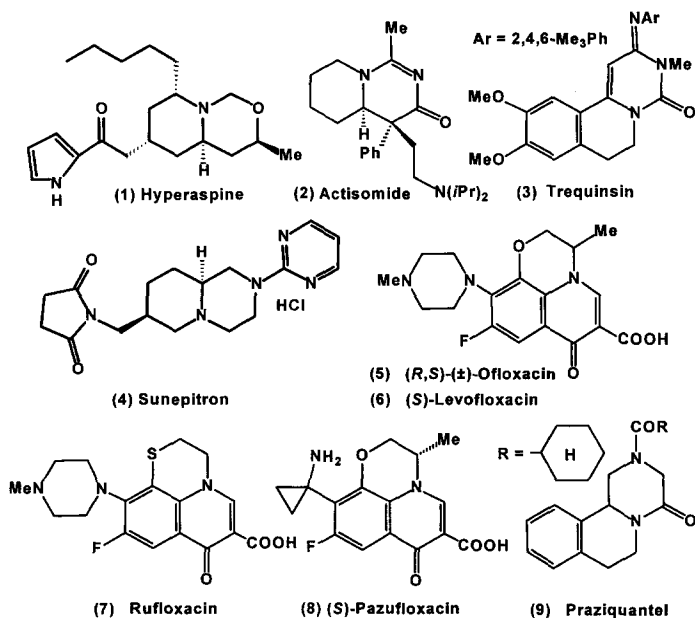
Perhydro derivatives of pyrido[1,2-b][1,2]oxazines are frequently applied in the total synthesis of various alkaloids to control the stereochemistry, and pyrido[1,2-c][1,3]oxazines and [1,3]oxazino[3,4-a]quinolines were also used in the stereoselective syntheses of different alkaloids. Perhydropyrido[1,2-c][1,3]oxazines and their benzologs are formed from 2-(2-hydroxyethyl) piperidines and from their benzologs to justify the stereochemistry of 2-(2-hydroxyethyl) derivatives. Different optically active pipecolic acids can be prepared via 4-phenylperhydropyrido[2,1-c][1,4]oxazin-1-ones.

Hyperaspine alkaloid (1) was isolated from ladybird beetle *Hyperaspis campestris*.

More than a dozen representatives of the above ring systems were introduced into the human therapy. Actisomide (2) and trequinsin (3) are used as antiarrhythmic and antihypertensive agents, respectively. Sunepitron (4), a  $\alpha_2$ -adrenoceptor antagonist, is under clinical trials for the treatment of anxiety and depression. Representatives of the third generation of antibacterial quinolone-3-carboxylic acids: the blockbuster ofloxacin (5), its levorotatory enantiomer, levofloxacin (6), and rifloxacin (7) have gained wide acceptance for the treatment of bacterial infections of the respiratory and urinary tracts, skin, and soft tissues, as well as sexually transmitted diseases, and pazufloxacin (8) is under development. Praziquantel (9) is widely applied for the treatment of schistosomes- and cestode-caused infection in both veterinary and human therapies (Scheme 4).

The pharmacological activities of other derivatives of these ring systems are examined intensively. Whereas other representatives of the above ring systems are patented as photographic sensitizers, catalysts for curing polyisocyanates, or dyes for acrylic nylon, polyester filters, photographic material.

In the following sections structure, thermodynamic aspects, theoretical calculations, spectroscopic properties, reactions, syntheses, and more briefly, utilization of the representatives of these ring systems are discussed.



Scheme 4

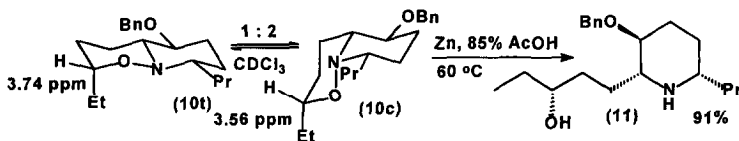


## II. Pyrido[1,2-*b*][1,2]oxazines and Their Benzologs

### A. STRUCTURE

#### 1. NMR Spectroscopy

$^1\text{H}$  NMR conformational studies revealed that  $2\alpha,4\alpha,8\alpha,5\beta$ -H-2-ethyl-5-benzyloxy-8-propylperhydropyrido[1,2-*b*][1,2]oxazine exists in  $\text{CDCl}_3$  in an equilibrium involving an 1 : 2 populations of *trans*- and *cis*-fused forms **10t** and **10c** due to nitrogen inversion (96JCS(P1)1113,S(P1)2077). The C(2) proton signals converged to a single resonance at  $60^\circ\text{C}$  in a pyridine- $d_5$  solution.  $^{13}\text{C}$  NMR data for **10t** and **10c** were also measured.



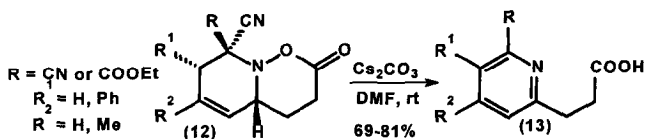
#### 2. X-ray Investigation

Stereostructure of ethyl *cis*-4*a*,7-H-7-phenyl-8-cyano-2-oxo-2,3,4,4*a*,7,8-hexahydropyrido[1,2-*b*][1,2]oxazine-8-carboxylate was confirmed by X-ray analyses. It justified a *trans* ring junction of the bicycle (00OL4007).

### B. REACTIVITY

#### 1. Ring Opening

Reductive N-O bond cleavage of perhydropyrido[1,2-*b*][1,2]oxazine **10** with Zn dust furnished 2-(3-hydroxypentyl)piperidine **11** (96JCS(P1)1113). Similarly,  $2\beta,4\alpha,5\alpha,7\beta,8\beta$ -H-5-benzyloxy-7-(*tert*-butyldiphenylsilyloxy)-2-[2-(methoxymethoxy)ethyl]-8-methylperhydropyrido[1,2-*b*][1,2]oxazine gave the respective ring-opened piperidine (00OL2955, 01JOC3338).

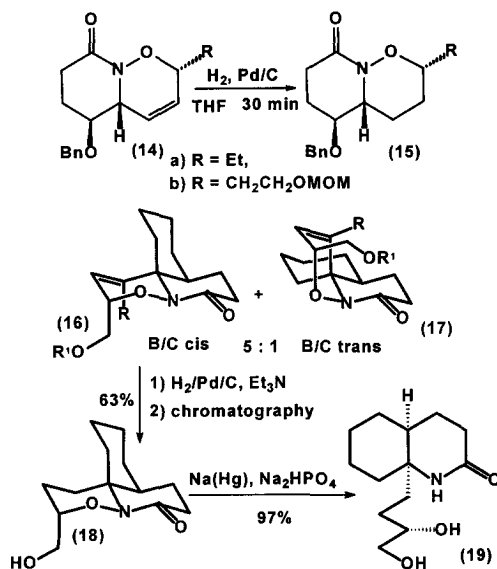


Aromatization of 8-(cyano or ethoxycarbonyl)-2-oxo-2,3,4,4a,7,8-hexahydropyrido[1,2-*b*][1,2]oxazine-8-carbonitriles **12** by treatment with  $\text{Cs}_2\text{CO}_3$  resulted the formation of (2-pyridyl)propionic acids **13** (00OL4007). Application of other bases, e.g. DBU,  $\text{NEt}_3$ , Dowex IX8-400 ion-exchange resin afforded (2-pyridyl)propionic acids in irreproducible or considerably lower yields.

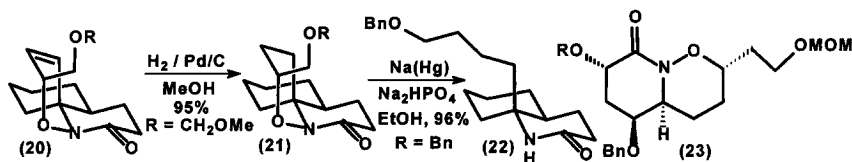
See further ring-opening reactions in Section II.B.2.

## 2. Hydrogenation, Reduction

Hydrogenation of 2,4a,5,6,7,8-hexahydropyrido[1,2-*b*][1,2]oxazin-8-ones **14** over 10% Pd/C catalyst gave perhydro derivatives **15** (96JCS(P1)1113, 00OL2955, 01JOC3338).



Catalytic hydrogenation of a mixture of [1,2]oxazino[3,2-*f*]quinolines **16** and **17** ( $\text{R} = \text{Br}$ ,  $\text{R}^1 = \text{Bn}$ ) over Pd/C catalyst, and chromatographic purification of the reaction product gave perhydro derivative **18**. Its N–O bond was cleaved by treatment with sodium amalgam to yield *cis*-perhydroquinolin-2-one **19** (00TL1205, 00JA4583). Similarly, methoxy-methoxy derivative **20** ( $\text{R} = \text{MOM}$ ) was reduced to perhydro derivative **21** ( $\text{R} = \text{MOM}$ ). The benzyloxy derivative **21** ( $\text{R} = \text{CH}_2\text{Ph}$ ) was converted to *trans*-fused perhydroquinolin-2-one **22** (00JA4583).

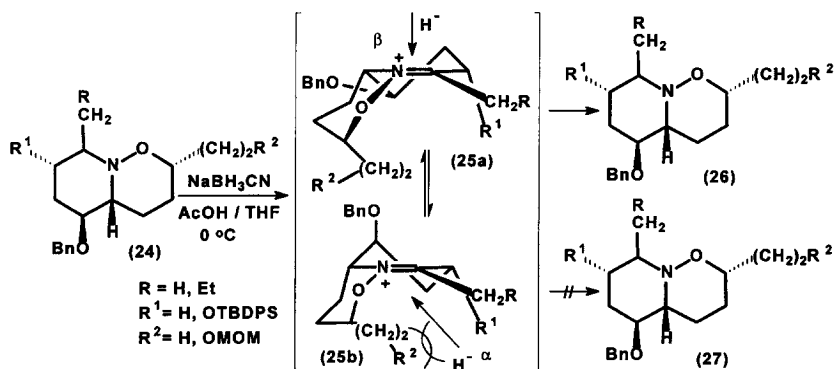


See further reduction in Section II.B.3.

### 3. Reactivity of Rings

A Grignard reaction of the 8-oxo group of perhydropyrido[1,2-*b*][1,2]oxazin-8-ones **15** (R = MeO) with PrMgBr; and **23** (R = OTBDPS) with MeMgBr with in THF at 0°C furnished bicyclic iminium salts **24**, which were immediately subjected to reduction with NaBH<sub>3</sub>CN to give stereospecifically a single stereoisomer **26** (96JCS(P1)1113). The stereoelectronically preferred axial attack by hydride occurred from the β face of the iminium moiety of the conformer **25a**. The alternative hydride approach from the α side of the iminium moiety of conformer **25b**, leading to the 8(*R*) diastereomer **27**, should be precluded due to the strong interaction between the 2-ethyl group and the incoming hydride species (Scheme 5). Similarly, 2α,4αβ,5α,7β,8β-H-5-benzyloxy-7-(*tert*-butyldiphenylsilyloxy)-2-[2-(methoxymethoxy)ethyl]-8-methylperhydropyrido[1,2-*b*][1,2]oxazine was prepared from the 8-oxo derivative by treatment with MeMgBr and then NaBH<sub>3</sub>CN in acidic medium (00OL2955, 01JOC3338).

Oxidation of the sodium enolate of **15b**, prepared by using NaHMDS, with (±)-2-phenylsulfonyl-3-phenyloxaziridine yielded the desired 7-hydroxy derivative **23** (R = H) and its C(7) epimer with a very low



Scheme 5

diastereoselectivity, 1.1 : 1 (00OL2955, 01JOC3338). When the lithium enolate of **15b**, formed by LiHMDS, was treated with (–)-[(8,8-dichlorocamphor-yl)sulfonyl]oxaziridine the diastereoselectivity increased to 17 : 1.

#### 4. Reactivity of Substituents Attached to Ring Carbon Atoms

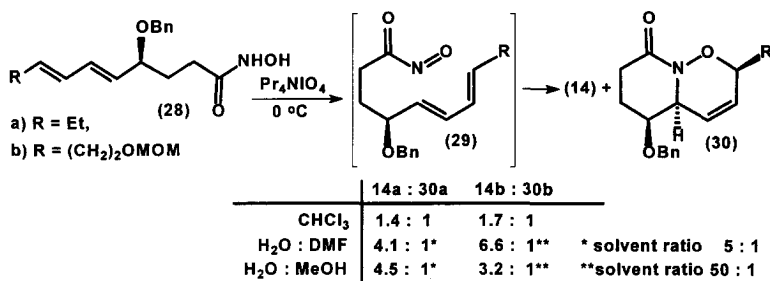
Hydroxy group of perhydropyrido[1,2-*b*][1,2]oxazin-8-one **23** (R = H) was protected with *t*-BuPh<sub>2</sub>SiCl in the presence of imidazole in DMF (00OL2955, 01JOC3338).

Methoxymethyl group of perhydro[1,2]oxazino[3,2-*j*]quinolin-6-one **21** (R = MOM) was converted to a hydroxymethyl group by treatment with a boiling mixture of conc. HCl and MeOH, and the hydroxymethyl group was benzylated with PhCH<sub>2</sub>Br in the presence of NaH and Bu<sub>4</sub>NI in DMF at room temperature (00JA4583).

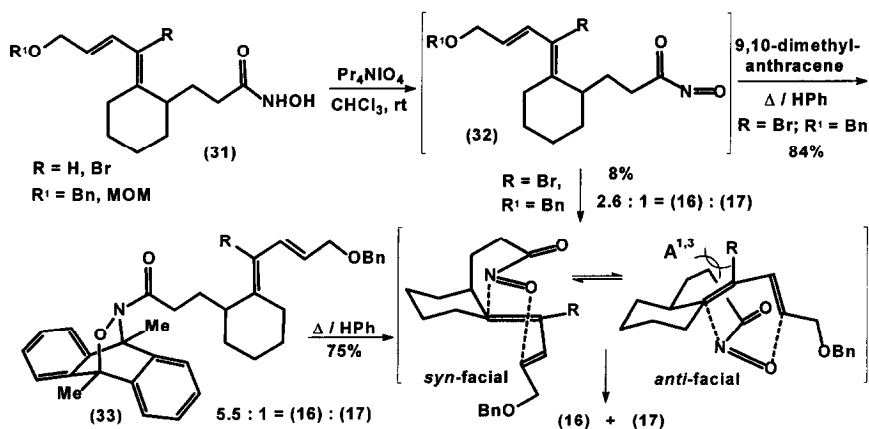
### C. SYNTHESSES

#### 1. Miscellaneous

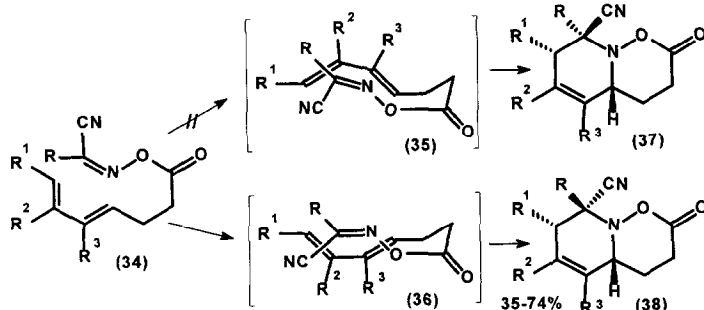
An intramolecular hetero Diels–Alder reaction of chiral *N*-acyl nitroso derivatives **29**, prepared from hydroxamic acids **28** by oxidation on treatment with Pr<sub>4</sub>NIO<sub>4</sub> in an aqueous medium, afforded a mixture of chiral pyrido[1,2-*b*][1,2]oxazin-8-ones **14** and **30** (96JCS(P1)1113, 00OL2955, 01JOC3338). Earlier it was clarified that the *trans* selectivity decreased in non-aqueous conditions (94TL595). The addition of  $\alpha$ -cyclodextrin (1 equiv.) increased the yield, but does not influenced the *trans/cis* selectivity (96JCS(P1)1113). The higher formation of **14** in aqueous medium was explained as a result of the hydrophobic effect on a reactant encapsulated in a cavity surrounded by a hydrogen network of water molecules (01JOC3338).



Whereas the acylnitroso derivative **32** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ), generated from hydroxamic acid **31** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ) with  $\text{Pr}_4\text{NIO}_4$ , provided a 2.6:1 racemic mixture of diastereomeric [1,2]oxazino[3,2-*f*]quinolin-6-ones **16** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ), and **17** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ), heating adduct **33** ( $R = \text{Br}$ ), prepared from **31** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ) under the previous conditions in the presence of 9,10-dimethylantracene, afforded a 5.5:1 racemic mixture of **16** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ) and **17** ( $R = \text{Br}$ ,  $R^1 = \text{Bn}$ ) in much higher yield (00TL1205, 00JA4583). When debromo derivative of **31** ( $R = \text{H}$ ,  $R^1 = \text{Bn}$ ) was used debromo derivative of **17** ( $R = \text{H}$ ,  $R^1 = \text{Bn}$ ) was the major product. Methoxymethoxy derivative of hydroxamic acid **31** ( $R = \text{H}$ ,  $R^1 = \text{MOM}$ ) afforded a 1:2.1 mixture of *cis* and *trans* tricycles **16** ( $R = \text{H}$ ,  $R^1 = \text{MOM}$ ) and **17** ( $R = \text{H}$ ,  $R^1 = \text{MOM}$ ) in 58% yield at 0°C (00JA4583). When the reaction was carried out in a 5:1 mixture of  $\text{H}_2\text{O}$  and an organic solvent (MeOH, DMF, and DMSO) the yield increased to 75–84%, and the selectivity to 4.5–4.8:1. In aqueous systems  $\text{Bu}_4\text{NIO}_4$  was also used as oxidation agent.



Heating acyl oximes **34** in refluxing toluene overnight promoted [4+2] intramolecular cycloaddition to give hexahydropyrido[1,2-*b*][1,2]oxazin-2-ones **38** (00OL4007). The cycloaddition could be promoted by high pressure (12 kbar) in similar yields at room temperature. It was assumed that cycloaddition occurred via a transition state **36** having the cyano group *endo* position. Molecular mechanics calculations indicate that pseudo boat conformation **36** with *endo*-cyano group is  $\sim 2.2$  kcal/mol more stable than the *exo*-cyano pseudo boat conformation **35**, which would lead to the alternative stereoisomer **37**. Cyclization of conformer **36** leads initially to a *cis*-fused ring system, which inverts to the *trans*-fused bicycle **38**.



## D. APPLICATIONS AND IMPORTANT COMPOUNDS

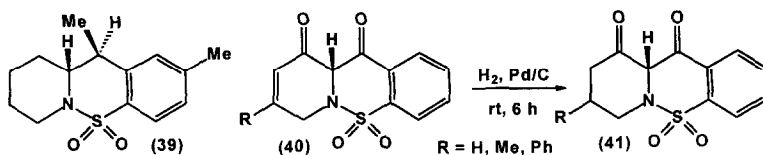
Perhydropyrido[1,2-*b*][1,2]oxazines are applied as key intermediates in a stereospecific total syntheses of (–)-pumiliotoxin C and 5-*epi*-pumiliotoxin C (96JCS(P1)1113), and the marine alkaloid (–)-lepadins A, B, C (00OL2955). (2-Pyridyl)propionic acids **13** can be regioselectively prepared via 2,3,4,4a,7,8-hexahydropyrido[1,2-*b*][1,2]oxazin-2-ones **12** (00OL4007).

## III. Pyrido[1,2-*b*][1,2]benzothiazines

### A. STRUCTURE

#### 1. X-ray Investigation

The absolute configuration of 2,11-dimethyl-7,8,9,10,10a,11-hexahydropyrido[1,2-*b*][1,2]benzothiazine 5,5-dioxide (**39**), isolated from the reaction of 2(*R*),1'(*S*)-1-tosyl-2-(1'-iodoethyl)piperidine with Bu<sub>3</sub>SnH, was determined by X-ray crystallographic analysis to be 10a(*R*),11(*S*) (81CSC121). This indicates that an inversion of the configuration at C(1') of the starting 2-(1'-iodoethyl)piperidine took place [although because of a change in priorities of the substituents at C(1') the corresponding symbol has remained *S*].



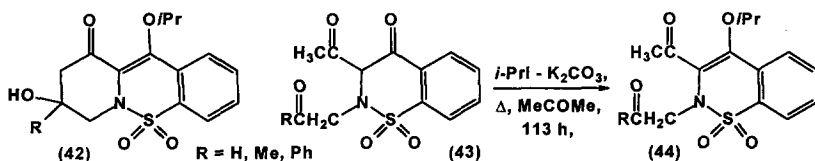
## B. REACTIVITY

### 1. Hydrogenation

Catalytic hydrogenation of 7,10,10*a*,11-tetrahydropyrido[1,2-*b*][1,2]benzothiazine-10,11-dione 5,5-dioxides **40** over 10% Pd/C afforded 7,8,9,10,10*a*,11-hexahydro derivatives **41** (67JMC223, 68USP3408347).

### 2. Reactivity of Substituents Attached to Ring Carbon Atoms

The treatment of 8-hydroxy-11-isopropoxy-7,8,9,10-tetrahydropyrido[1,2-*b*][1,2]benzothiazin-10-ones **42** with conc. H<sub>2</sub>SO<sub>4</sub> at ambient temperature yielded 7,10,10*a*,11-tetrahydropyrido[1,2-*b*][1,2]benzothiazin-9,10-diones **40** (67JMC223, 68USP3408347).



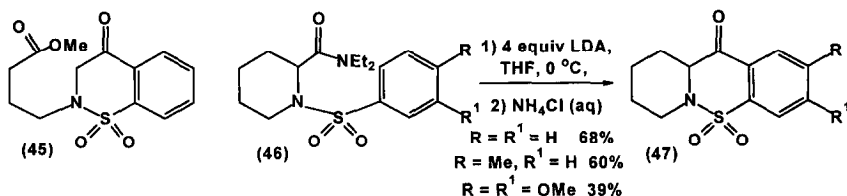
## C. SYNTHESIS

### 1. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6+0( $\gamma$ )]

Ring closure of 3-acetyl-2-(2-oxoethyl)-3,4-dihydro-2*H*-1,2-benzothiazin-4-ones **43** (R = Me, Ph) to 8-hydroxy-7,8,9,10-tetrahydropyrido[1,2-*b*][1,2]benzothiazine-10-one 5,5-dioxides (**42**, R = Me, Ph) failed under acidic conditions (with conc. H<sub>2</sub>SO<sub>4</sub> at room temperature or conc. HBr at reflux), or on the treatment with NaNH<sub>2</sub> and LiNH<sub>2</sub> in liquid NH<sub>3</sub>, and with NaH in DMF (67JMC223). However, cyclization of **43** (R = Me, Ph) was successful, via **44** (R = Me, Ph), on the treatment with *i*-PrI and K<sub>2</sub>CO<sub>3</sub> to give tricyclic derivatives **42** (R = Me, Ph) (67JMC223, 68USP3408347). Cyclization of 3-acetyl-4-(2-propoxy)-2*H*-1,2-benzothiazine-2-acetaldehyde 1,1-dioxide (**44**, R = H) on the action of K<sub>2</sub>CO<sub>3</sub> in boiling acetone for 2.5 h afforded 8-hydroxy-7,8,9,10-tetrahydropyrido[1,2-*b*][1,2]benzothiazine-10-one 5,5-dioxide (**42**, R = H) (67JMC223, 68USP3408347).

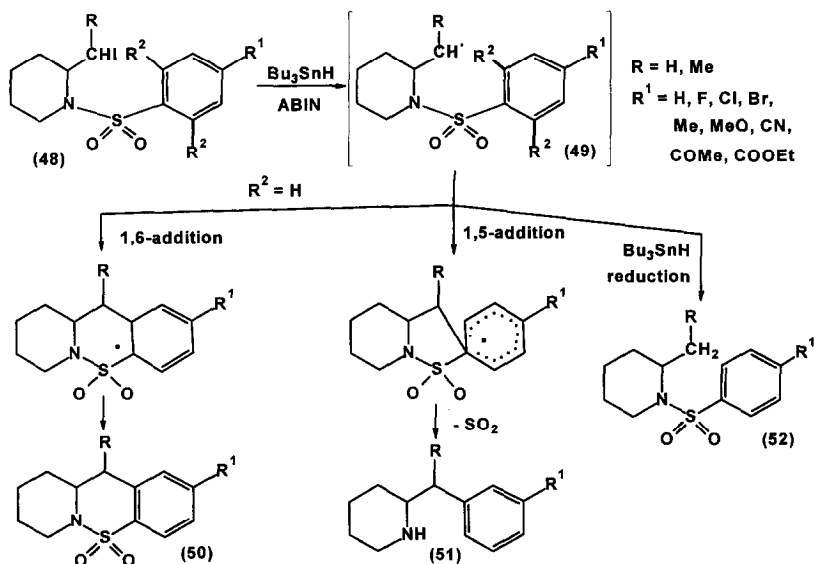
Preparation of 7,8,9,10,10*a*,11-hexahydropyrido[1,2-*b*][1,2]benzothiazine-10,11-dione 5,5-dioxide (**41**, R = H) by cyclization of 2-(3-methoxycarbonylpropyl)-3,4-dihydro-2*H*-1,2-benzothiazin-4-one 1,1-dioxide (**45**) on the

action of NaH in benzene or DMF, that of NaOEt in EtOH, or that of LiNH<sub>2</sub> in liquid NH<sub>3</sub> was unsuccessful (67JMC223).



Treatment of 1-arylsulfonylpipercolinamides **46** with excess LDA gave pyrido[1,2-*b*][1,2]benzothiazine 5,5-dioxides **47** in a carbanion-mediated reaction (97SL1079, 98MI2). When the reaction mixture of **46** (R = Me, R<sup>1</sup> = H) was quenched with MeI an ethyl derivative **47** (R = Et, R<sup>1</sup> = H) was obtained.

Treatment of 1-arylsulfonyl-2-(1-iodoalkyl)piperidines **48** (R<sup>2</sup> = H) with 2.7 equiv. of Bu<sub>3</sub>SnH in the presence of azobisisobutyronitrile (ABIN) furnished a mixture of 7,8,9,10,10*a*,11-hexahydropyrido[1,2-*b*][1,2]benzothiazine 5,5-dioxides **50**, 2-benzylpiperidines **51** and 1-arylsulfonyl-2-alkylpiperidines **52** in a radical process (Scheme 6) (77TL631, 78JCS(CC)166, 80JCS(CC)142). The yield of 7,8,9,10,10*a*,11-hexahydropyrido[1,2-*b*][1,2]



Scheme 6



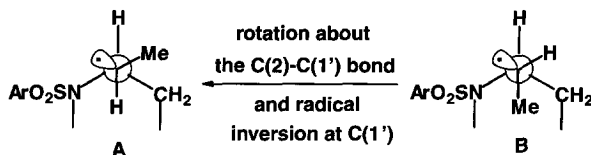


Fig. 1

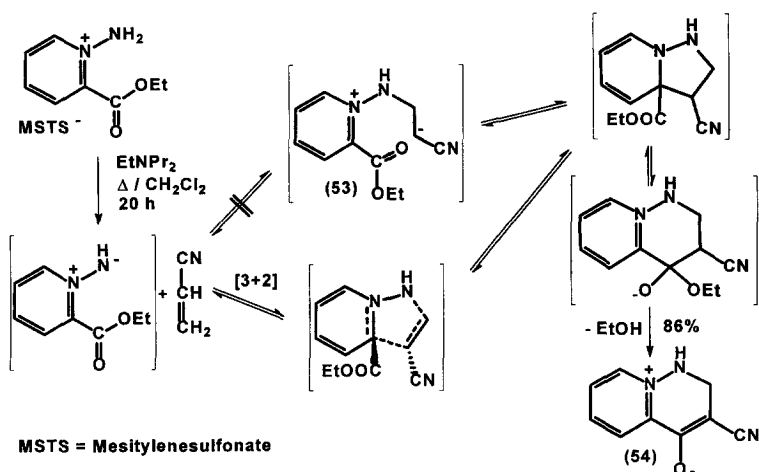
benzothiazine 5,5-dioxides **50** decreased with increasing ratio of  $\text{Bu}_3\text{SnH}$  and increasing reaction temperature (77TL631). In boiling benzene **48** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ) afforded 45% of **50** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Me}$ ), 32% of **51** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Me}$ ) and 23% of **52** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Me}$ ) with  $\text{Bu}_3\text{SnH}$  in the presence of ABIN, whereas 64% of **50** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Me}$ ) and 25% of **52** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Me}$ ) formed with  $(\text{Bu}_3\text{Sn})_2$  in the presence of di-*tert*-butyl peroxalate (77TL631). Presence of methyl group in ortho positions in **48** ( $\text{R}^2 = \text{Me}$ ) prevented the 1,6-addition process (77TL631). (10*aR*,11*S*)-2,11-Dimethyl-7,8,9,10,10*a*,11*i*-hexahydropyrido[1,2-*b*][1,2]benzothiazine (**50**,  $\text{R} = \text{R}^1 = \text{Me}$ ) formed from both (2*R*,1'*S*)-1-[(4-methylphenyl)sulfonyl]-2-(1-iodoethyl)piperidine (**48**,  $\text{R} = \text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ) (with complete inversion at C-1') and its (2*R*,1'*R*) diastereomer (with complete retention at C-1') (80JCS(CC)142). Formation of **50** and **51** ( $\text{R} = \text{R}^1 = \text{Me}$ ) from the intermediate **49** ( $\text{R} = \text{R}^1 = \text{Me}$ ) may take place from either conformation **A** [from (2*R*,1'*S*) isomer] or **B** [from (2*R*,1'*R*) isomer] (Fig. 1), but upon ring closure of **B** a severe steric interaction would be present in the transition state of the addition, therefore interconversion of conformer **B** to **A** happened by rotation about the C(2)–C(1') bond and radical inversion at C(1') (80JCS(CC)142).

## IV. Pyrido[1,2-*b*]pyridazines and Their Benzo Derivatives

### A. STRUCTURE

#### 1. Theoretical Calculation

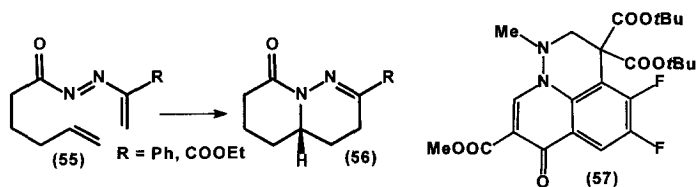
A theoretical study based on PM3 frontier molecular orbital (FMO) and potential energy surface (PES) analysis at the RHF/6-31+G\* level was performed to examine the reaction of 1-amino-2-ethoxycarbonylpyridinium mesitylenesulfonate and acrylonitrile in the presence of Hünig's base leading to the formation of 3-cyano-4-hydroxy-1,2-dihydropyrido[1,2-*b*]pyridazinium inner salt (**54**) (99JOC9001). The calculations indicated that both the



Scheme 7

[3+2]cycloaddition reaction and the ring expansion occurred in a concerted way rather than through a stepwise mechanism via a zwitterionic intermediate **53** (Scheme 7).

*Ab initio* Hartree–Fock and density functional theory calculations were performed to study the transition state geometry in intramolecular Diels–Alder cycloaddition of azoalkenes **55** to give 2-substituted 3,4,4a,5,6,7-hexahydro-8*H*-pyrido[1,2-*b*]pyridazin-8-ones **56** (01MI7).



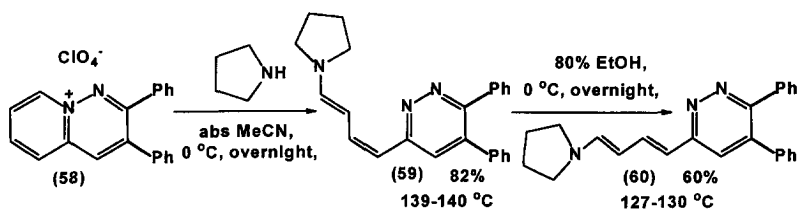
## 2. X-ray Investigations

X-ray investigations on 3,3-bis(*tert*-butoxycarbonyl)-4,5-difluoro-1-methyl-7-oxo-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate **57** revealed, that 1-methyl group is perpendicular to the plane of the 4-quinolone moiety (96BCJ1371).

## B. REACTIVITY

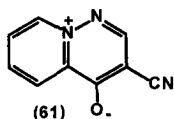
## 1. Ring Opening

Ring-opening of 2,3-diphenylpyrido[1,2-*b*]pyridazinium salt (**58**) with pyrrolidine in abs. MeCN afforded 1-*cis*-3-*trans* diene **59**, whereas in protic solvent the primary product **59** underwent a rapid isomerization into the 1-*trans*-3-*trans* diene **60** (96JOC4423). Similar ring-opening of 7-methyl derivative of **58** did not occur, even under forcing conditions (01CPH77). The different reactivities were explained as the steric hindrance caused by methyl group on the basis of the positron annihilation lifetime measurements.



## 2. Oxidation

Pyrido[1,2-*b*]pyridazinium inner salt **61** was prepared from 1,2-dihydropyrido[1,2-*b*]pyridazinium inner salt **54** by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in CH<sub>2</sub>Cl<sub>2</sub> at room temperature in 95% yield (99JOC9001).

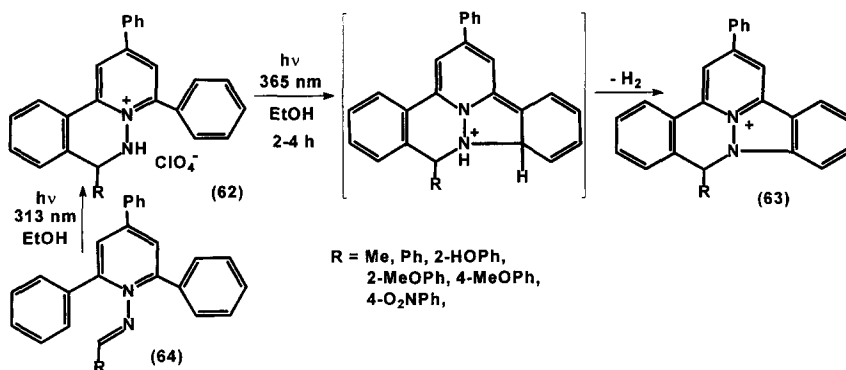


## 3. Reactivity of Substituents Attached to Ring Carbon Atoms

Acidic hydrolysis of 2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-3,3,8-tricarboxylate **57** with a mixture of 6*N* HCl and AcOH at 100 °C yielded 4,5-difluoro-1-methyl-7-oxo-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-3,8-dicarboxylic acid (96BCJ1371).

4. *Rearrangement*

Irradiating 7-substituted 2,4-diphenyl-6,7-dihydropyrido[2,1-*a*]phthalazinium perchlorates **62** in EtOH by 365 nm afforded pentacyclic derivatives **63** (94MI1).



## C. SYNTHESIS

1. *By Formation of One Bond  $\gamma$  to the Bridgehead Nitrogen Atom [6+0( $\gamma$ )]*

Photocyclization of 2,4,6-triphenylpyridinium salts **64** by irradiating by 313 nm gave 7-substituted 2,4-diphenyl-6,7-dihydropyrido[2,1-*a*]phthalazinium salts **62** (94MI1).

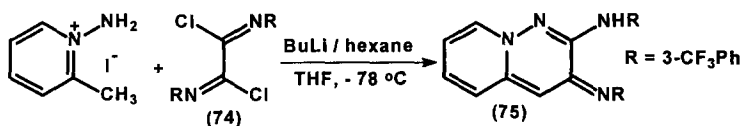
2. *By Fragments of Two Bonds from [4+2] Atom Fragments*

Pyrido[1,2-*a*]pyridazinium bromide was obtained, when the reaction mixture of 1-amino-2-methylpyridinium mesitylenesulfonate and [1,4]dioxane-2,3-diol was treated with 48% HBr in DMF in the presence of NEt<sub>3</sub> at 70°C (00T2469).

The reaction of 1-amino-2-methylpyridinium tosylate and its 5-methyl derivative with benzil in the presence of NEt<sub>3</sub> in boiling MeCN, and the treatment of the reaction mixture with 60% HClO<sub>4</sub> and 40% HBF<sub>4</sub> gave 2,3-diphenylpyrido[1,2-*b*]pyridazinium salt (**58**) (96JOC4423) and its 7-methyl derivative (01CPH77), respectively.



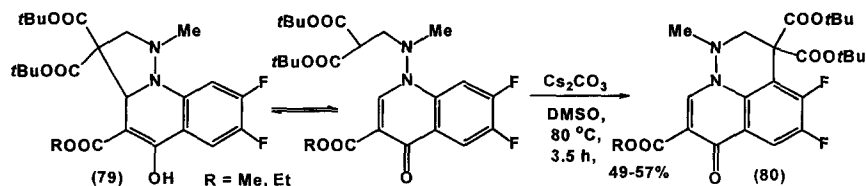
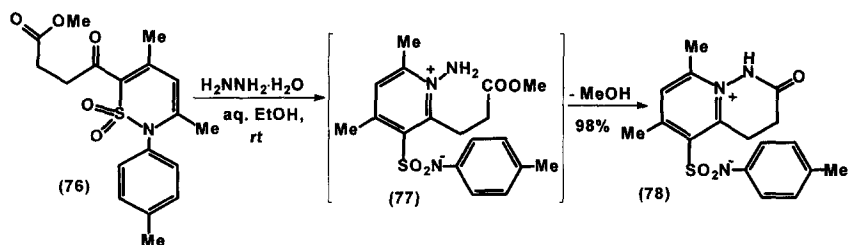
vinyl sulfone under similar conditions yielded a mixture containing oxidized betains **71** and **72** (99JOC9001). 3-Cyano-4-hydroxypyridazino[1,6-*a*]quinolinium betaine (**73**) could be isolated from the reaction mixture of 1-amino-2-ethoxycarbonylquinolinium mesitylsulfonate and acrylonitrile in a few percent. 2-Amino-1-ethoxycarbonylisoquinolinium salt with acrylonitrile afforded only pyrazolo[5,1-*a*]isoquinoline derivative.



In the presence of BuLi 1-amino-2-methylpyridinium iodide and imidoyl chloride **74** yielded 2-(substituted amino)-3-(substituted imino)-3*H*-pyrido[1,2-*b*]pyridazine **75** (01JHC205).

### 3. Ring Transformation

Zwitterionic 2-oxo-1,2,3,4-tetrahydropyrido[1,2-*b*]pyridazine **78** was obtained from 6-(3-methoxycarbonylpropionyl)-1,1-dioxo-1,2-thiazine **76** with hydrazine hydrate via pyridinium betaine **77** (99JPR37).



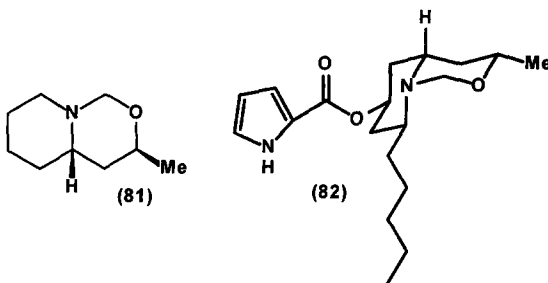
Treatment of pyrazolo[1,5-*a*]quinoline-3,3,4-tricarboxylates **79** with  $\text{Cs}_2\text{CO}_3$  afforded 2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-3,3,8-tricarboxylates **80** (96BCJ1371).

## V. Pyrido[1,2-*c*][1,3]oxazines and Their Benzologs

### A. STRUCTURE

#### 1. Infrared Spectroscopy

The presence of the Bohlmann bands (2812, 2778 and 2756/cm) in the infrared spectrum of 3-methylperhydropyrido[1,2-*c*][1,3]oxazine **81** identifies the *trans*-fused conformation of the bicycle (97TA109).



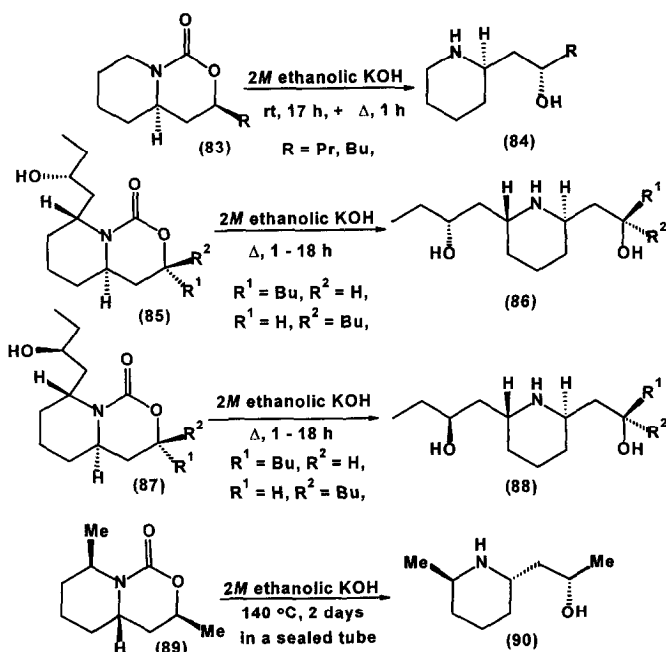
#### 2. NMR Spectroscopy

The relative stereochemistry of hyperaspine (**1**) was determined by 2D NMR and MS methods. It has a *cis*-fused bicyclic conformation **82** (01TL4621). The *trans*-fused one is disfavored by an axial pentyl group at C(8) and by a destabilising dipole–dipole interaction between the N and O atoms, which does not exist in the alternative *cis* conformation.

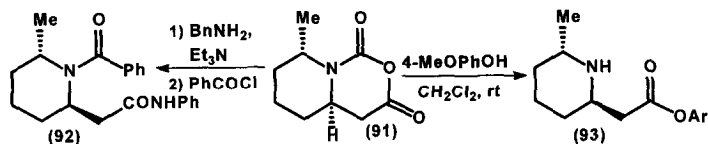
### B. REACTIVITY

#### 1. Ring Opening

Treatment of perhydropyrido[1,2-*c*][1,3]oxazin-1-ones **83**, **85**, and **87** with 2 M ethanolic KOH afforded 2-(2-hydroxyalkyl)piperidines **84**, **86**, and **88** (96CJC2434). (+)-9-Epi-6-epipinidinol (**90**) was obtained similarly from 3,8-dimethylperhydropyrido[1,2-*c*][1,3]oxazin-1-one **89** (98T13505).



Reaction of 8-methylperhydropyrido[1,2-*c*][1,3]oxazine-1,3-dione **91** with  $PhCH_2NH_2$  then  $PhCOCl$  and 4-methoxyphenol afforded ring-opened products **92** and **93**, respectively (00JA11009).



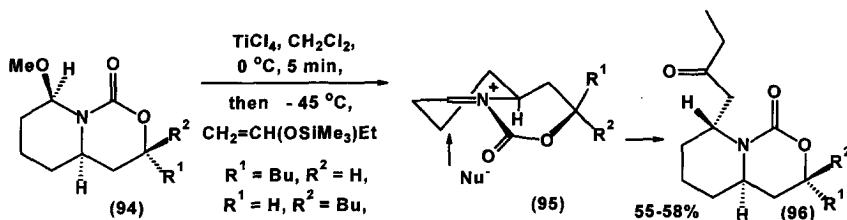
## 2. Reactivity of Ring Carbon Atoms

3,3-[Di-(2-propyl)]perhydropyrido[1,2-*c*][1,3]oxazin-1-one was lithiated with *s*-BuLi in the presence of TMEDA 200 times less efficiently, than the five-membered lower homolog 3,3-[di(2-propyl)]perhydropyrido[1,2-*c*][1,3]oxazolin-1-one, and approximately five times more efficiently than 1-(*tert*-butoxycarbonyl)piperidine (01JA315).

The nucleophilic displacement of 9-methoxy group of perhydropyrido[1,2-*c*][1,3]oxazin-1-ones **94** was performed by treatment with an excess of 2-(trimethylsilyloxy)but-1-ene in the presence of  $TiCl_4$  to give 9-(2-oxobutyl) derivatives **96** (96CJC2434). The high stereoselectivity observed in

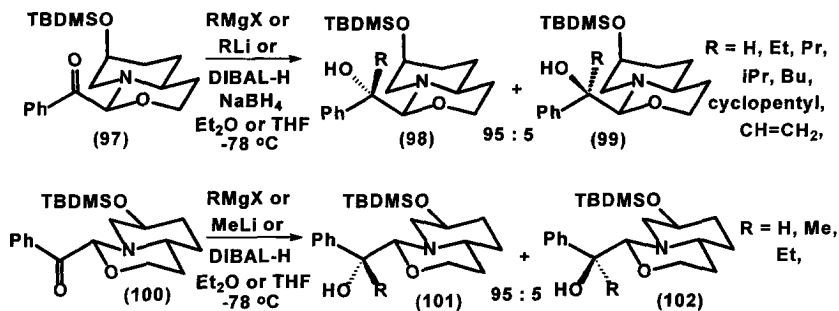


favor of the *trans*-4*a*,9-H compounds **96** results from the stereoelectronically preferred axial attack of the nucleophile on the *N*-acylinium ion **95**. No formation of *cis*-4*a*,9-H-9-(2-oxobutyl) derivative was detected.



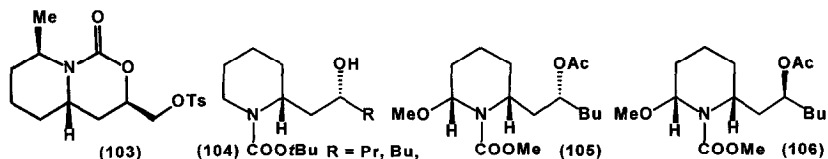
### 3. Reactivity of Substituents Attached to Ring Carbon Atoms

Reduction of the side chain keto group in 9-(2-oxobutyl)perhydropyrido[1,2-*c*][1,3]oxazin-1-ones **96** with  $\text{NaBH}_4$  in MeOH at ambient temperature afforded an epimeric mixtures of 9-(2-hydroxybutyl) derivatives **85** and **87** (96CJC2434). The epimers were separated by means of flash chromatography.



Reaction of 1-benzoylperhydropyrido[1,2-*c*][1,3]oxazines **97** and **100** with Grignard reagents, organolithium reagents or reducing agents afforded usually a diastereomeric mixtures of alcohols **98** and **99**, furthermore **101** and **102**, respectively (99MI19). No reaction occurred with *t*-BuMgCl in the case of **97**. The isomeric ratio of **98** and **99** was 70 : 30 and 53 : 47 in the case of *i*-PrMgBr and cyclopentylmagnesium chloride, respectively.

8-Methyl-3-(tosyloxymethyl)perhydropyrido[1,2-*c*][1,3]oxazin-1-one **103** was detosylated by treatment with  $\text{LiEt}_3\text{H}$  (Super-Hydride<sup>®</sup>) (98T13505).

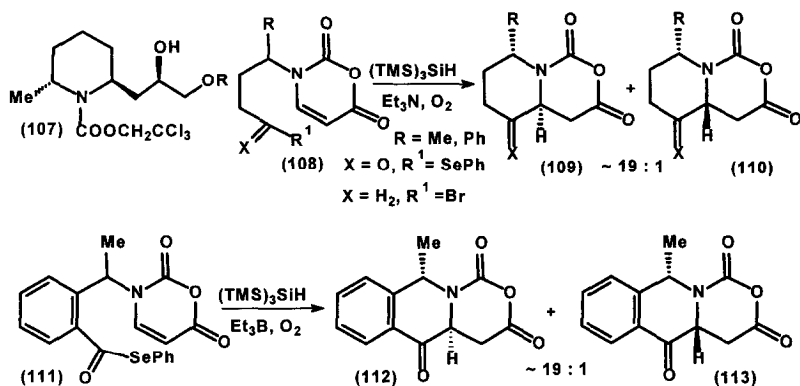


## C. SYNTHESIS

1. By Formation of One Bond  $\beta$  to the Bridgehead Nitrogen Atom [6+0( $\beta$ )]

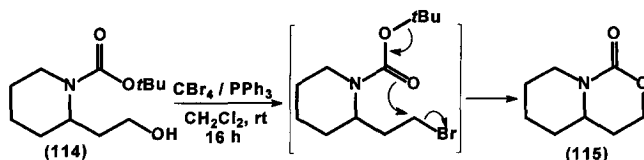
3-Substituted perhydropyrido[1,2-*c*][1,3]oxazines **83** were obtained by the cyclization of 1-(*tert*-butoxycarbonyl)-2-(2-hydroxyalkyl)piperidines **104** in pyridine on the action of  $\text{MeSO}_2\text{Cl}$  at room temperature (96CJC2434). Cyclization of *cis*-2,6-H-1-(methoxycarbonyl)-2-(2-acetoxyhexyl)-9-methoxypiperidines **105** and **106** in THF in the presence of  $\text{KOt-Bu}$  yielded 3-butyl-9-methoxyperhydropyrido[1,2-*c*][1,3]oxazin-1-ones **94**. Treatment of 1-(*tert*-butoxycarbonyl)-2-[2-hydroxy-2,2-di(2-propyl)ethyl]piperidine with  $\text{NaH}$  in boiling THF yielded 3,3-di(2-propyl)perhydropyrido[1,2-*c*][1,3]oxazin-1-one (01JA315).

Treatment of 2-(2,3-dihydroxypropyl)piperidine **107** ( $\text{R}=\text{H}$ ) with  $\text{Bu}_2\text{SnO}$ , than with 4-MePh $\text{SO}_2\text{Cl}$  gave a mixture of perhydropyrido[1,2-*c*][1,3]oxazin-1-one **103** and tosylated piperidine **107** ( $\text{R}=\text{Ts}$ ) in 62 and 37% yields, respectively (98T13505).



Radical cyclization of acyl selenides **108** ( $\text{X}=\text{O}$ ,  $\text{R}^1=\text{SePh}$ ) and alkyl bromides **108** ( $\text{X}=\text{H}_2$ ,  $\text{R}^1=\text{Br}$ ) with  $(\text{TMS})_3\text{SiH}$  and  $\text{Et}_3\text{B}$  in the presence of air furnished perhydropyrido[2,1-*c*][1,3]oxazine-1,3,5-triones **109** and -diones **110** ( $\text{X}=\text{O}$ ,  $\text{H}_2$ ), as a mixture of diastereoisomers, favoring

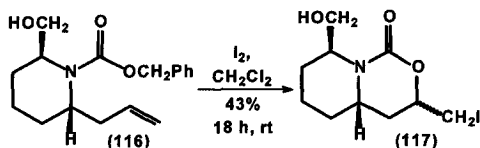
**109** (00JA11009). Similarly, aryl acyl selenide **111** gave a mixture of diastereoisomers **112** and **113**.



Perhydropyrido[1,2-*c*][1,3]oxazin-1-one (**115**) was obtained, when 1-*tert*-butoxycarbonyl-2-(2-hydroxyethyl)piperidine (**114**) was treated with  $\text{CBr}_4$  in the presence of  $\text{PPh}_3$  (99BMCL2621). Mesilate of **114** also afforded **115** on standing.

### 2. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6+0( $\gamma$ )]

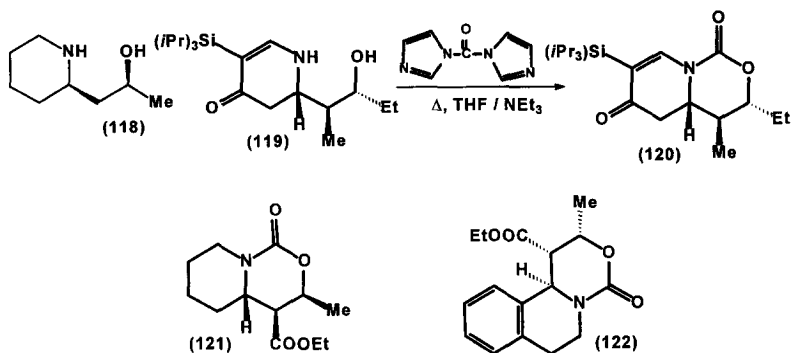
Treatment of piperidine **116** with  $\text{I}_2$  yielded a 1:1 diastereomeric mixture of 3-iodomethylperhydropyrido[1,2-*c*][1,3]oxazin-1-ones **117** (99JOC8402).



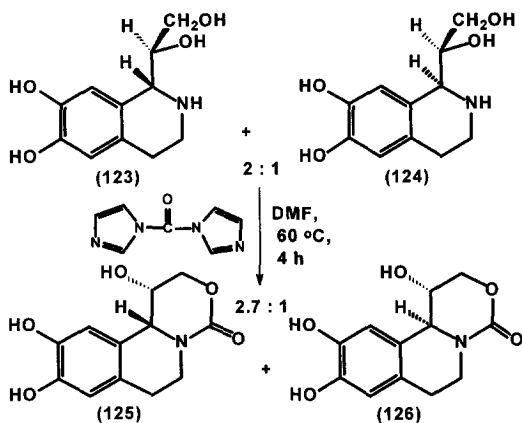
### 3. By Formation of Two Bonds from [5+1] Atom Fragments

Reaction of (+)-sedridine (**118**) and a 37% aqueous solution of  $\text{CH}_2\text{O}$  in MeOH at room temperature gave 3-methylperhydropyrido[1,2-*c*][1,3]oxazine (**81**) (97TA109). Similarly, reaction of andrachcinidine alkaloid, *cis*-2,6-*H*-2-(2-oxopropyl)-6-(2-hydroxypentyl)piperidine with 1.5% methanolic formaldehyde solution afforded *cis*-3,4*a*,9-*H*-9-(2-oxopropyl)-3-propylperhydropyrido[1,2-*c*][1,3]oxazine (00MI71).

Reaction of (2*S*,5*S*)- and (2*R*,5*S*)-2-[5-(*tert*-butyldimethylsilyloxy)piperidin-2-yl]ethanols with phenylglyoxal monohydrate in the presence of 4 Å molecular sieves in boiling  $\text{CH}_2\text{Cl}_2$  overnight gave (1*S*,4*aS*,7*R*)- and (2*R*,4*aR*,7*R*)-1-benzoyl-7-(*tert*-butyldimethylsilyloxy)perhydropyrido[1,2-*c*][1,3]oxazines **97** and **100**, respectively, in good yield (99MI19). Both products were accompanied by unidentified minor isomers.



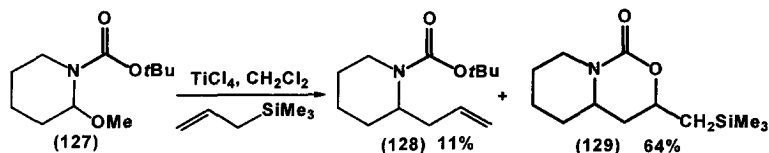
Reaction of tetrahydropyridin-4-one **119** and 1,1'-carbonyldiimidazole furnished 1,3,4,4a,5,6-hexahydropyrido[1,2-*c*][1,3]oxazine-1,6-dione **120** (99JA2651). Similarly, pyrido[1,2-*c*][1,3]oxazine-1-one **121** and [1,3]oxazino[4,3-*a*]isoquinoline-4-one **122** were prepared from the respective 2-(2-hydroxypropyl)piperidine and 1-(2-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline (99JOC3790). Reaction of a 2:1 diastereomeric mixture of 1-(1,2-dihydroxyethyl)-6,7-dihydroxy-1,2,3,4-dihydroisoquinolines **123** and **124** with 1,1'-carbonyldiimidazole gave a 2.7:1 mixture of 1,9,10-trihydroxy-1,6,7,11*b*-tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline-4-ones **125** and **126**, which were separated on preparative TLC plate (99BMC2525).



Reaction of 8-(1-hydroxyethyl)-1,2,3,4,5,6,7,8-octahydroquinoline-2-one and PhCHO in benzene in the presence of *p*TSA gave 1-methyl-3-phenyl-6,7,8,9,10,10*a*-1*H*,5*H*-hexahydropyrido[3,2,1-*ij*][3,1]benzoxazin-5-one (01MI13).

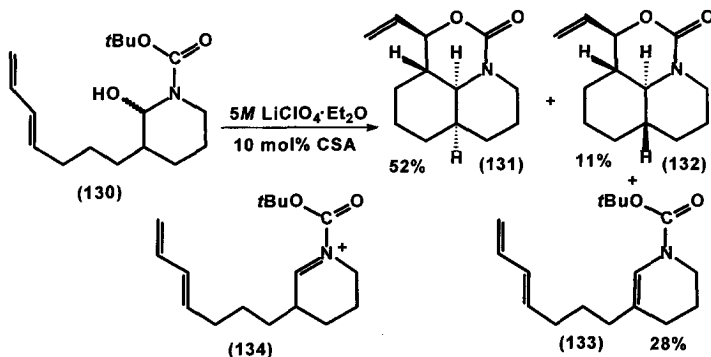
#### 4. By Formation of Two Bonds from [4+2] Atom Fragments

Treatment of 2-methoxy-1-*tert*-butoxycarbonylpiperidine (**127**) with allyltrimethylsilane and  $\text{TiCl}_4$  gave a mixture of 2-allyl-1-*tert*-butoxycarbonylpiperidine (**128**) and 3-[(trimethylsilyl)methyl]perhydropyrido[1,2-*c*][1,3]oxazin-1-one (**129**) (97JCS(P1)2163).



#### 5. Miscellaneous

Treatment of 0.01 M solution of piperidine **130** in  $\text{Et}_2\text{O}$  containing 5.0 M  $\text{LiClO}_4$  with 10 mol% camphorsulfonic acid (CSA) gave a mixture of perhydropyrido[3,2,1-*ij*][3,1]-benzoxazines **131** and **132** together with 1,4,5,6-tetrahydropyridine **133** (99JOC6041). Reexposure of **133** to 5.0 M  $\text{LiClO}_4 \cdot \text{Et}_2\text{O}$ , containing 10 mol% CSA, for 26 h afforded 28% yield of **131** and **132** in a ratio of 4:1 along with recovered **133** (55%). The result explained that tricyclic derivatives **131** and **132** was formed from iminium ion **134** by a concerted intramolecular [4+2] cycloaddition. The product formation **131** and **132** was rationalized by transition state analysis of iminium ion **134**.



Hyperaspine (**1**) was isolated from *H. campestris* by extraction with MeOH and subsequent flash chromatography (01TL4621).

## D. APPLICATION AND IMPORTANT COMPOUNDS

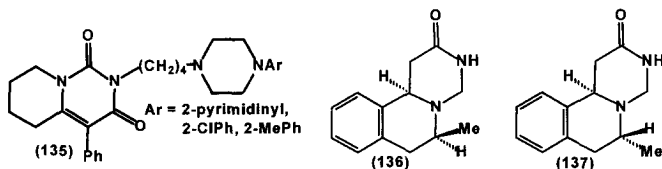
Hyperaspine (**1**), a perhydropyrido[1,2-*c*][1,3]oxazine alkaloid was isolated from the ladybird beetle *H. campestris* (01TL4621). 9-Epi-6-epipinidinol (**90**), a piperidine alkaloid, was prepared from a perhydropyrido[1,2-*c*][1,3]oxazin-1-one derivative (98T13505). Perhydropyrido[1,2-*c*][1,3]oxazin-1-ones were used to prepare 2,6-disubstituted piperidines (96CJC2434).

## VI. Pyrido[1,2-*c*]pyrimidines and Their Benzologs

### A. STRUCTURE

#### 1. Thermodynamic Aspects

Acidimetric, spectrophotometric and HPLC assays were developed for determination of 2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones **135** (98MI33). Its solubility properties were also characterized. Resolution of the enantiomers of 4-phenyl-2-{4-[4-(2-pyrimidinyl)piperazinyl]butyl}perhydropyrido[1,2-*c*]pyrimidine-1,3-dione was achieved on *heptakis*(2-*N,N*-dimethylcarbamoyl)- $\beta$ -cyclodextrines (01JC(A)249).



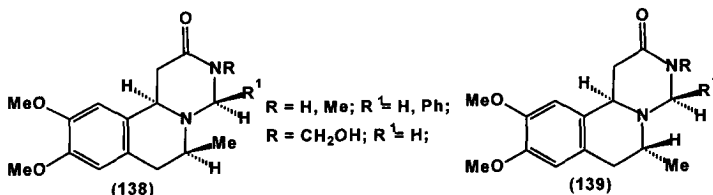
#### 2. Theoretical Calculations

Semiempirical PM3 MO calculations were performed on eight 4-aryl-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1,3-diones and on their dimers (00JPO213). In all of the calculated structures the aromatic ring is almost perpendicular to the plane of the pyrido[1,2-*c*]pyrimidin-1,3-dione fragment, which is in accordance with the X-ray data for 4-(4-methylphenyl) derivative.

Conformational studies of *cis*-6,11*b*-H- and *trans*-6,11*b*-H-6-methyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrimido[6,1-*a*]isoquinolin-2-ones (**136** and **137**) by means of the MM2 method implemented in the HyperChem 4.5 suggested, that in the lowest-energy conformations heterocyclic moiety adopted *trans*-fused ring annelation in both cases, with a pseudo-equatorial and -axial methyl group, respectively (97LA1165).

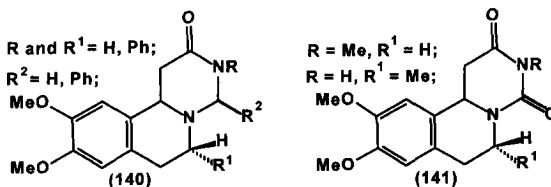
### 3. NMR Spectroscopy

Characteristic  $^1\text{H}$  NMR data of (4a*R*,5*S*)- and (4a*S*,5*R*)-2-substituted 5- $\{[N-(tert\text{-butoxycarbonyl})\text{-L-tryptophyl}]\text{amino}\}$ perhydropyrido[1,2-*c*]pyrimidine-1,3-diones were tabulated (01JMC2219).  $^{13}\text{C}$  CPMASS NMR data of 4-(4-methoxyphenyl)perhydropyrido[1,2-*c*]pyrimidine were reported (00JST73).  $^{13}\text{C}$  NMR data were reported for eight 4-aryl-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1,3-diones in the solid state and in  $\text{CDCl}_3$  solution (00JPO213). The structure of 4-aryl-3,4-dihydro-2*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones and their 2,3,5,6,7,8-hexahydro derivatives were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (99JHC389). Conformational analysis of 6-methyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrimido[6,1-*a*]isoquinolin-2-ones **138** and **139** were carried out by  $^1\text{H}$  and  $^{13}\text{C}$  NMR studies (97LA1165).



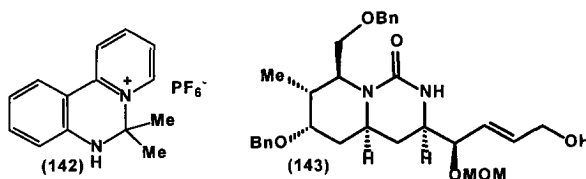
### 4. Mass Spectrometry

The mass spectral fragmentations of 9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrimido[6,1-*a*]isoquinolin-2-ones **140** and -2,4-diones **141**, under electron ionization (at 70 eV) were examined by metastable ion analysis, a collision-induced dissociation technique and exact mass measurement (97RCM1879). Methyl substituent on N(3) in **140** ( $\text{R} = \text{Me}$ ) had a larger effect on both the fragmentation and on the peak intensities, than a methyl substituent on C(6) ( $\text{R}' = \text{Me}$ ). The ionized molecules of **140** ( $\text{R}^2 = \text{H}$ ) were rather stable, whereas 4-phenyl substitution on C(4) of **140** ( $\text{R}^2 = \text{Ph}$ ) promoted the fragmentations of the molecular ions. The hexahydro-1*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones **141** were more stable, than the hexahydro-1*H*-pyrimido[6,1-*a*]isoquinolin-2-ones **140**, and the molecular ions formed base peaks.



## 5. X-ray Investigations

The structures of 6,6-dimethyl-6,7-dihydropyrido[1,2-*c*]quinazolinium salt (**142**) (97AJC109), and 6-methyl-9,10-dimethoxy-4-phenyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrimido[6,1-*a*]isoquinolin-2-one (**139**, R = H, R<sup>1</sup> = Ph) (97LA1165) were established by X-ray crystallographic analysis. In compound **139** (R = H, R<sup>1</sup> = Ph) 4-phenyl group occupies a *pseudo*-equatorial position, and 6-methyl group has a *pseudo*-axial orientation.

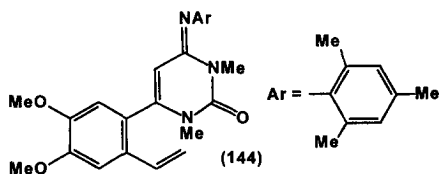


The stereostructure of perhydropyrido[1,2-*c*]pyrimidine **143** was determined by X-ray crystallography (01JA8851). Solid state structures of 4-(2-chlorophenyl) (99JHC389), 4-(4-fluorophenyl), 4-(4-chlorophenyl) (00ZN(B)1089), 4-(4-methylphenyl) (00JPO213) derivatives of 2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-dione and 4-(4-methoxyphenyl)-perhydropyrido[1,2-*c*]pyrimidine (00JST73) were determined by X-ray investigations. The aryl substituent is almost perpendicular to the plane of the bicycle. X-ray investigations on 4-phenyl-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-dione revealed that the saturated pyridine ring adopted a sofa conformation and the pyrimidine-1,3-dione moiety was nearly planar (99AX(C)1950). The phenyl ring was twisted with respect to the pyrimidine-1,3-dione fragment.

## B. REACTIVITY

## 1. Ring Opening

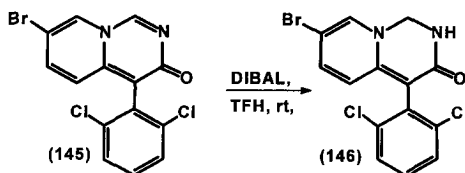
Pyrimidinone **144** was obtained from trequinsin (**3**) on the action of NaH in DMF at 70 °C for 15 min, followed by the addition of MeI at 10 °C for 1 h (97IJC(B)349).



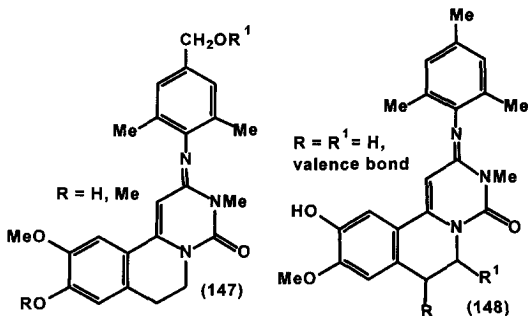


## 2. Reduction and Oxidation

Reduction of 3*H*-pyrido[1,2-*c*]pyrimidin-3-one **145** with DIBAL-H gave 1,2-dihydro derivative **146** (98MIP11, 00USP6147080). Catalytic hydrogenation of 4-aryl-2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones in AcOH over PtO<sub>2</sub> and Pd/C (10%) under 60 atm of hydrogen pressure at 50 °C for 10–15 h yielded 2,3,5,6,7,8-hexahydro derivatives (99JHC389). Catalytic hydrogenation of 2-(3- and 4-nitrophenyl)-5-(*tert*-butoxycarbonylamino)perhydropyrido[1,2-*c*]pyrimidine-1,3-dione over 10% Pd/C catalyst in MeOH in the presence of 37% H<sub>2</sub>CO yielded the respective dimethylamino derivative (01JMC2219).



Reduction of 2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3,7-trione and 7-chloro-6-formyl-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-dione with NaBH<sub>4</sub> in THF in the presence of 60% aqueous solution of NaOH gave 7-hydroxy and 7-chloro-6-hydroxymethyl derivatives, respectively (01MI28).



Selective oxidation of 4'-methyl group of trequinsin (**3**) and its 9-desmethyl derivative with DDQ in benzene after 20 h, and then treatment with ZnCl<sub>2</sub> in MeOH for another 20 h yielded 2-[(2,6-dimethyl-4-methoxymethylphenyl)imino] derivatives **147** (R = H, Me; R<sup>1</sup> = Me) (98IJC(B)1). Oxidation of **3** with DDQ in boiling benzene for 39 h gave its 2-[(2,6-dimethyl-4-hydroxymethylphenyl)imino] derivative **147** (R = Me, R<sup>1</sup> = H) in 2% yield after chromatographic work-up. Treatment of an 1:2 complex of **3** and DDQ in boiling dioxane with Zn(OAc)<sub>2</sub> for 43 h gave

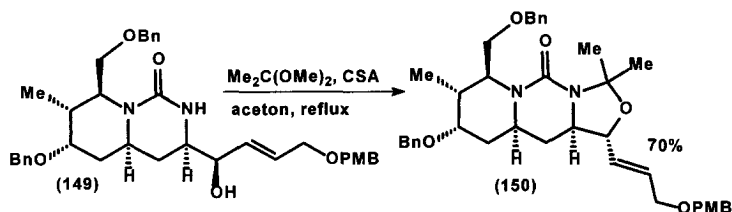
2-[(2,6-dimethyl-4-formylphenyl)imino] derivative in 8% yield. This compound was also obtained in 63% yield from 4'-hydroxymethyl derivative **147** ( $R = \text{Me}$ ,  $R^1 = \text{H}$ ) by oxidation with pyridinium chlorochromate in  $\text{CH}_2\text{Cl}_2$ . Oxidation of 2-[(2,4,6-trimethylphenyl)imino]-3-methyl-9-methoxy-10-hydroxy-3,4,6,7-tetrahydro-2*H*-pyrido[6,1-*a*]isoquinolin-4-one **148** ( $R = R^1 = \text{H}$ ) with DDQ in benzene afforded 3,4-dihydro derivative **148** ( $R = R^1 = \text{valence bond}$ ) in 14% yield.

See further oxidation reaction in Section IV.B.3.

### 3. Reactivity of Ring Nitrogen

Perhydropyrido[1,2-*c*]pyrimidine was N-arylated with 6-bromo-1-(2-propyl)indole in the presence of DBU,  $\text{NaOt-Bu}$ ,  $(t\text{-Bu})_3\text{P}$ , and  $\text{Pd}(\text{OAc})_2$  in boiling xylene (01MIP6).

Reaction of perhydropyrido[1,2-*c*]pyrimidin-1-one **149** with  $\text{Me}_2\text{C}(\text{OMe})_2$  in the presence of CSA afforded tricyclic derivative **150** (01JA8851).



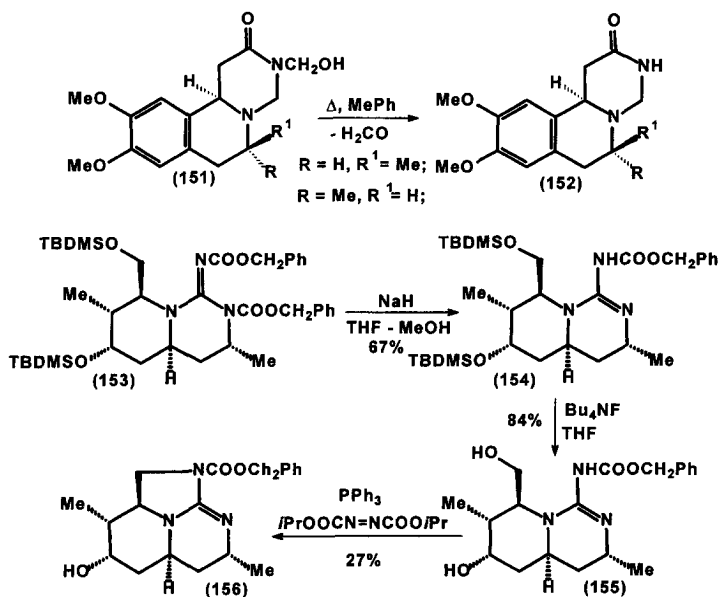
9,10-Dimethoxy-2-(arylimino)-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones were N-alkylated with *N*-( $\omega$ -bromoalkyl)phthalimides in the presence of  $\text{K}_2\text{CO}_3$  and catalytic amount of  $\text{I}_2$  in boiling 2-butanone in 13–67% yields (00MIP19).

Reaction of 8,9-difluoro-5-methyl-6,7-dihydro-5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-dione with 2,4-dinitrophenylhydroxylamine in the presence of  $\text{NaH}$  in a 1:1 mixture of dioxan and DMF at 60–80°C afforded 2-amino derivative (01MIP23).

Treatment of 2-[(4-methoxyphenyl)methyl] derivative of 2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-diones with  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  afforded 2-unsubstituted derivatives. A 2-unsubstituted derivative was N-alkylated with 4-methoxybenzyl chloride in DMF in the presence of  $\text{K}_2\text{CO}_3$  at 50°C (01MIP22).

#### 4. Reactivity of Substituents Attached to Ring Nitrogen Atom

Heating 3-hydroxymethyl derivative of epimeric 6-methyl-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones **151** resulted in the formation of 3-unsubstituted derivatives **152** by loss of CH<sub>2</sub>O (97LA1165).



The N(2) atom of 1-iminoperhydropyrido[1,2-*c*]pyrimidine **153** was selectively deprotected by treatment with NaH to yield 1-amino-4,4*a*,5,6,7,8-hexahydropyrido[1,2-*c*]pyrimidine **154** (00TL1849).

3-( $\omega$ -Aminoalkyl)-9,10-dimethoxy-2-(arylimino)-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones were obtained from 3-[( $\omega$ -phthaliminoalkyl)] derivatives with H<sub>2</sub>NNH<sub>2</sub>·H<sub>2</sub>O in a mixture of EtOH and CHCl<sub>3</sub> (00MIP19). The free amino group was reacted with NaCN in acidified H<sub>2</sub>O at 80 °C, with isocyanates in toluene at room temperature, with *N*-methyl-1-(methylthio)-2-nitroethanamine and 1,1-bis(methylthio)-2-nitroethylene in boiling toluene, with *N,N'*-di-(*tert*-butoxycarbonyl)thiourea in DMF in the presence of 1-methyl-2-chloropyridinium iodide and NEt<sub>3</sub> at room temperature, with 2-methyl-1-nitro-2-isothioureia in EtOH at 70 °C, with dimethyl *N*-cyanodithioiminocarbonate in toluene at 90 °C to yield 3-(*N*-carbamoyl- $\omega$ -aminoalkyl), 3-[*N*-(*N'*-substituted carbamoyl)-2-aminoethyl], 3-[*N*-(1-methylamino-2-nitrovinyl)-2-aminoethyl], 3-[*N*-(1-methylthio-2-nitrovinyl)-2-aminoethyl], 3-[*N*-(*N'*-nitro)-2-guanidinoethyl],

3-[*N*-(*N'*,*N''*-di-*tert*-butoxycarbonyl)-2-guanidinoethyl], 3-[*N*-(*S*-methyl)isothioureidoethyl] derivatives, respectively. Methylthio group of 3-[*N*-(1-methylthio-2-nitrovinyl) and 3-[*N*-(*S*-methyl)isothioureidoethyl] moieties was changed for an substituted amino group with methylamine, 2-propylamine, and dimethylamine. A 3-(guanidinoethyl) derivative was obtained from 3-[*N*-(*N'*,*N''*-di-*tert*-butoxycarbonyl)-2-guanidinoethyl] derivative by treatment with TFA in CH<sub>2</sub>Cl<sub>2</sub> at room temperature.

### 5. Reactivity of Ring Carbon Atoms

Vilsmeier-Haack formylation of 7-hydroxy-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-dione with POCl<sub>3</sub>/DMF gave 7-chloro-6-formyl-2,3-dihydro-1*H*,5*H* derivative. Boiling a toluene solution of the aforementioned 7-hydroxy derivative in the presence of *p*TSA yielded dehydrated 2,3-dihydro derivative (01MI28).

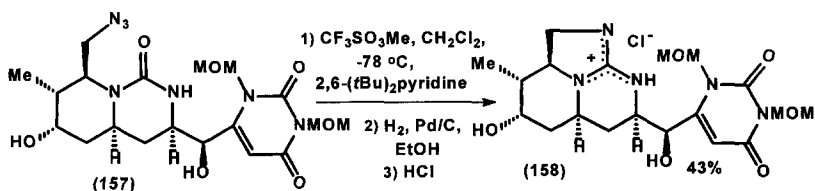
8-Fluoro atom of 2-amino-8,9-difluoro-5-methyl-6,7-dihydro-5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-dione was replaced by 3-substituted pyrrolidines in the presence of NEt<sub>3</sub> in DMSO at 110 °C for 18 h (01MIP23).

Reaction of 7-bromo-4-(2,6-dichlorophenyl)-1,2-dihydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-one (**146**) and PhSH in boiling xylene in the presence of Bu<sub>3</sub>SnOMe and (Ph<sub>3</sub>P)<sub>4</sub>Pd gave 7-(phenylthio) derivative in 52% yield (98MIP11, 00USP6147080).

Reaction of 2-chloro-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones with liquid NH<sub>3</sub> in a pressure bomb at 85 °C for 4 h, and with primary and secondary amines in boiling CHCl<sub>3</sub> (98MIP15), and anilines in boiling *i*-PrOH (00MI17) yielded 2-amino-6,7-dihydro derivatives or their 2,3,6,7-tetrahydro-2-imino tautomers.

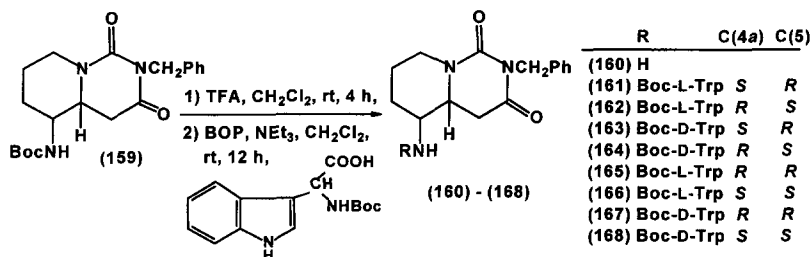
### 6. Reactivity of Substituents Attached to Ring Carbon Atoms

The *tert*-butyldimethylsilyl groups of pyrido[1,2-*c*]pyrimidine **154** was eliminated with Bu<sub>4</sub>NF to afford 6-hydroxy-8-hydroxymethyl derivative **155** (00TL1849). Compound **155** gave tricyclic derivative **156** under Mitsunobu conditions.

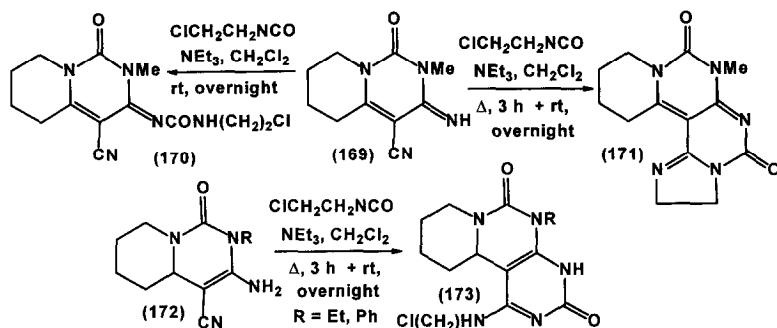


Treatment of 8-azidomethylperhydropyrido[1,2-*c*]pyrimidin-1-one **157** with methyl triflate and catalytic hydrogenation of the azide group led to the formation of tricyclic guanidine derivative **158** (01JA8851). Hydroxy group of **149** was protected with methoxymethyl chloride, and the *p*-methoxybenzyl protecting group (PMB) was eliminated by treatment with DDQ.

2-Aryloxy-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones formed in the reaction of 2-chloro derivative and phenols in the presence of  $K_2CO_3$  in DMF at 90 °C for 2–4.5 h or in boiling 2-PrOH for 6–24 h (00MIP20). When 2-isobutylphenol was used the reaction was carried out in the presence of BuLi in THF at –78 °C.

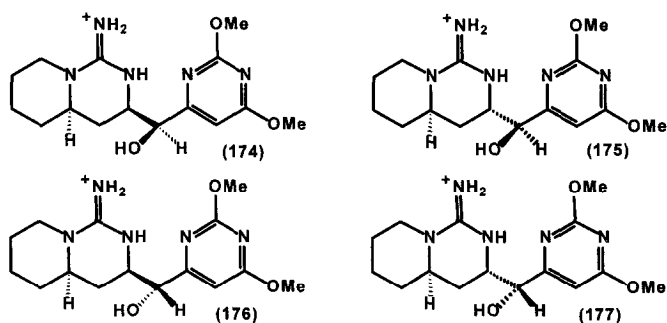


Treatment of (4*aR*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]perhydropyrido[1,2-*c*]pyrimidine-1,3-dione **159** [C(4*a*)*R*,C(5)*S*] (97JMC3402) and other 2-substituted derivatives (01JMC2219) with TFA yielded 5-amino derivatives (e.g. **160** [R = H, C(4*a*)*R*,C(5)*S*]), which were acylated with Boc-L- or Boc-D-tryptophane in the presence of benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and  $NEt_3$  to afford a 4 : 1 diastereomeric mixture of e.g. **161**, **162** and **163**, **164**, respectively. These results indicated that about 20% of racemization had occurred during under the above conditions (97JMC3402). Similarly, a 4 : 1 mixture of **165**, **166** and **167**, **168** were obtained from compound **159** [C(4*a*)*R*,C(5)*R*] with Boc-L- and Boc-D-tryptophane. *tert*-Butoxycarbonyl group of 5-(*tert*-butoxycarbonylamino)perhydropyrido[1,2-*c*]pyrimidine-1,3-diones was removed by treatment with TFA in  $CH_2Cl_2$ . The free amino group was acylated with different amino acids in the presence of BOP and  $NEt_3$  (97MIP16, 98MI63), and was reacted with  $PhNCO$  (97MIP16). Amino group of 2-amino-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one was acylated with  $PhCOCl$  in  $CHCl_3$  in the presence of 4-dimethylaminopyridine (98MIP15).



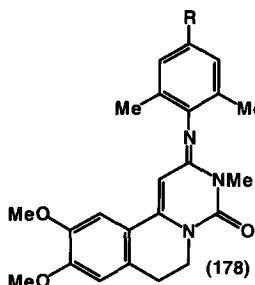
Reaction of 4-cyano-3-imino-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one **169** with 2-chloroethyl isocyanate at ambient temperature and under reflux gave *N*-acylated **170** and tetracyclic derivative **171**, respectively (95MI1). Similar reaction of 3-amino-4-cyano-2,4a5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-ones **172** afforded tricyclic compounds **173**.

Hydrolysis of 3-[(2,6-dimethoxy-4-pyrimidinyl)hydroxymethyl]perhydropyrido[1,2-*c*]pyrimidin-1-iminium salts **174–177** in boiling conc. HCl afforded the appropriate 3-[(2-hydroxy-6-oxo-1,6-dihydropyrimidin-4-yl)hydroxymethyl] derivative (98TL7021, 00JA5017).



Demethylation of trequinsin (**3**) with a 65 : 35 mixture of AcOH and 48% HBr at 115°C for 3 h gave mainly 10-hydroxyl derivatives **148** ( $\text{R} = \text{R}^1 = \text{H}$ ), which was accompanied by traces of its 9-hydroxyl and 9,10-dihydroxy derivatives. In boiling 48% HBr for 2 h its 9,10-dihydroxy derivative formed in 63% yield (98IJC(B)1). 9-Methoxy group of **3** and that of its 2-[(2,6-dimethyl-4-carboxyphenyl)imino] derivative **178** ( $\text{R} = \text{COOH}$ ) was selectively demethylated by the treatment with 60% NaOH and EtSH in HMPA. Treatment of **3** with pyridine HCl in boiling pyridine for 20 min afforded its 9,10-dihydroxy-3-desmethyl derivative in 65% yield. 4'-Hydroxymethyl

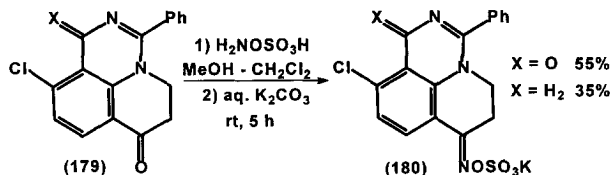
derivative **147** ( $R = R^1 = H$ ) was obtained from 9-hydroxy-10-methoxy-2-(2,6-dimethyl-4-methoxymethylphenyl)imino]-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one (**147**,  $R = H$ ,  $R^1 = Me$ ) in boiling 2*N* HCl for 93 h in 53% yield. 4'-Carboxy metabolite **178** ( $R = COOH$ ) of **3** was prepared from its 2-[(2,6-dimethyl-4-cyanophenyl)imino] derivative **178** ( $R = CN$ ) by hydrolysis with 20% aqueous NaOH in boiling EtOH for 39 h and from 2-[(2,6-dimethyl-4-formylphenyl)imino] derivative **178** ( $R = CHO$ ) by oxidation with a mixture of AgNO<sub>3</sub> and NaOH in boiling 30% aqueous EtOH for 45 h (98IJC(B)1). The 4'-cyano derivative was prepared in 80% yield from the 4'-formyl derivative **178** ( $R = CHO$ ) via oxime **178** ( $R = CH=NOH$ ), which was dehydrated in boiling Ac<sub>2</sub>O.



10-Benzoyloxy derivative was prepared from 10-hydroxy-9-methoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one **148** ( $R = R^1 = H$ ) with PhCH<sub>2</sub>Br in the presence of K<sub>2</sub>CO<sub>3</sub> in boiling acetone (98IJC(B)1). Hydroxy group of 9,10-dimethoxy-2-(2-hydroxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one was acylated with PhCOCl (98MIP15).

Treatment of a pyrido[3,2,1-*ij*]quinazoline-1,3-dione containing a {[*tert*-butyl(dimethyl)silyl]oxy}methyl side chain with Bu<sub>4</sub>NF in THF at room temperature gave a HOCH<sub>2</sub> derivative which was O-alkylated with PhCH<sub>2</sub>Br in THF in the presence of 60% aqueous NaOH solution at 60°C. Hydroxymethyl group were oxidized with SO<sub>3</sub>-pyridine complex in DMSO in the presence of NEt<sub>3</sub>, and with pyridinium dichromate in HCONH<sub>2</sub> overnight at room temperature to an aldehyde and carboxylic acid, respectively. Hydroxymethyl group was converted to a ClCH<sub>2</sub> and a BrCH<sub>2</sub> group by treatment with SOCl<sub>2</sub> and with CBr<sub>4</sub>/Ph<sub>3</sub>P, respectively in MeCN. Halomethyl moiety was reacted with 40% aqueous HNMe<sub>2</sub> solution, *N*-benzylmethylamine and NaN<sub>3</sub> in DMF to give (disubstituted amino)methyl and N<sub>3</sub>CH<sub>2</sub> derivatives, respectively. N<sub>3</sub>CH<sub>2</sub> group was converted to an H<sub>2</sub>NCH<sub>2</sub> group by treatment with (PhO)<sub>3</sub>P in aqueous THF. Amino moiety of H<sub>2</sub>NCH<sub>2</sub> group was acylated with carboxylic acids and α-amino acids (01MI28).

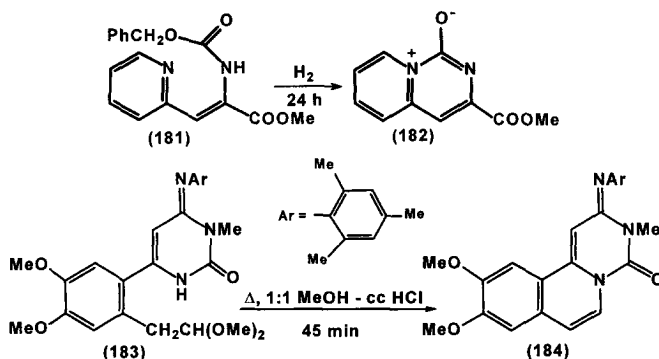
7-Oxime-*O*-sulfonic acid potassium salts of pyrido[3,2,1-*ij*]quinazolines **180** ( $X = H_2, O$ ) were obtained from 7-oxo derivatives **179** ( $X = H_2, O$ ) by reacting with hydroxylamino-*O*-sulfonic acid, then with  $K_2CO_3$  (98EJM763). Reaction of 2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3,7-trione with  $HONH_2 \cdot HCl$  in boiling EtOH in the presence of NaOAc afforded 7-oxime derivative (01MI28).



## C. SYNTHESIS

### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6+0( $\alpha$ )]

It was assumed that pyridine derivative **181** yielded pyrido[1,2-*c*]pyrimidine betaine **182** under catalytic hydrogenation conditions over (*S,S*)-Et-DuPhoS-Ph catalyst (99TL1211). 6,7-Dehydro derivative **184** of trequinsin (**3**) was obtained from pyrimidinone **183** by heating in an 1 : 1 mixture of MeOH and conc. HCl under reflux (97IJC(B)349).

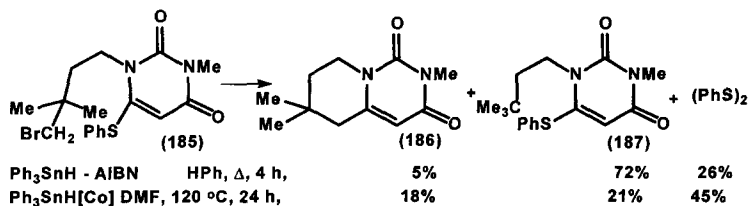


### 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6+0( $\beta$ )]

When 1-(4-bromo-3,3-dimethylbutyl)-3-methyl-6-phenylthiouracil (**185**) was allowed to react with  $Ph_3SnH$  in the absence and presence of cobaloxime [Co] complex reaction mixtures were obtained, containing a few



percent of 2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-dione **186** and debrominated pyrimidine **187** (97JCS(P1)3591).

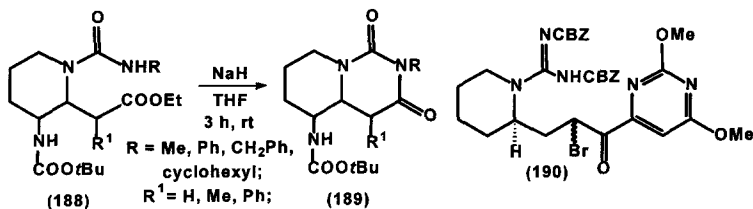


2-Chloro-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one was obtained by the cyclization of *N*-[2-(3,4-dimethoxyphenyl)ethyl]barbituric acid on the action of boiling  $\text{POCl}_3$  in 62% yield (98MIP15, 00MIP19,P20).

2,3,6,7-Tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-diones were prepared by the cyclization of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydroquinoline-8-carboxamide on the action of 60% aqueous  $\text{NaOH}$  solution in THF at  $50^\circ\text{C}$  (01MI28).

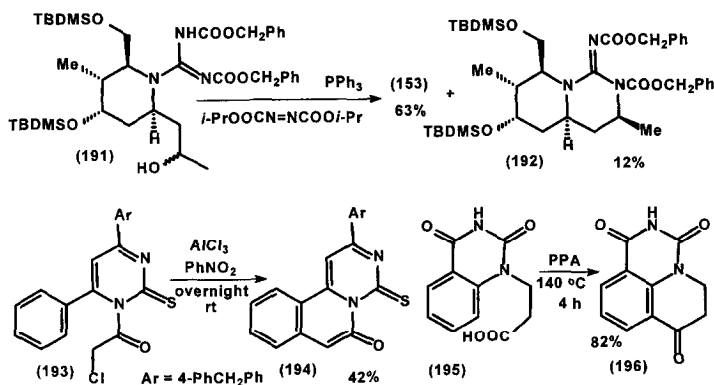
### 3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6+0( $\gamma$ )]

Cyclization of 1-(*N*-substituted aminocarbonyl)-3-[(*tert*-butoxycarbonyl)amino]- and -3-[[*N*-(*tert*-butoxycarbonyl)tryptophyl]amino]-2-(ethoxycarbonylmethyl)piperidines (e.g. **188**) on the action of  $\text{NaH}$  gave 2-substituted 5-(substituted amino)perhydropyrido[1,2-*c*]pyrimidine-1,3-diones (e.g. **159** and **189**) (97JMC3402, 97MIP16, 98MI63, 01JMC2219). Cyclization could be also carried out in the presence of DBU (01JMC2219).



Under the circumstance of catalytic hydrogenation of piperidine derivatives **190** in MeOH over  $\text{Pd/C}$  catalyst afforded an isomeric mixture of perhydropyrido[1,2-*c*]pyrimidines **174–177** (98TL7021, 00JA5017). The main product was **174** (66%).

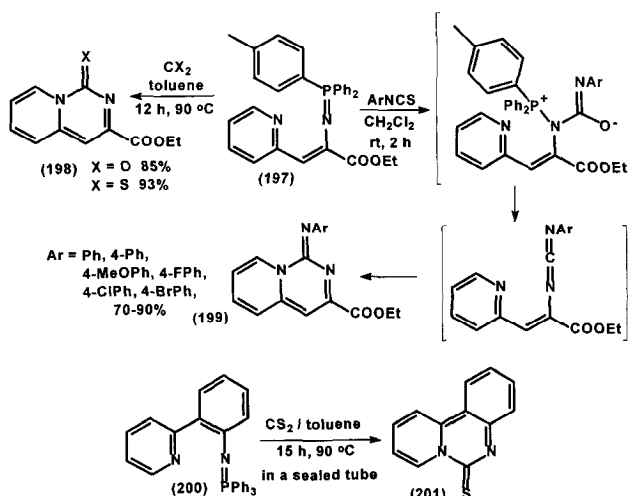
An 1 : 5 epimeric mixture of piperidine derivatives **191** was cyclized under Mitsunobu condition to afford a mixture of 1-iminoperhydropyrido[1,2-*c*]pyrimidines **153** and **192** (00TL1849).



Treatment of pyrimidine-2-thione **193** with  $\text{AlCl}_3$  in  $\text{PhNO}_2$  yielded 2-(4-benzylphenyl)-6-oxo-6,7-dihydro-4*H*-pyrido[6,1-*a*]isoquinolin-4-thione (**194**) (98MI47). Cyclization of 1-(2-carboxyethyl)-1,2,3,4-tetrahydroquinazoline-2,4-dione (**195**) in PPA afforded 1,2,3,5,6,7-hexahydropyrimido[3,2,1-*ij*]quinazoline-1,3,7-trione (**196**) (97CHE96).

#### 4. By Formation of Two Bonds from [5+1] Atom Fragments

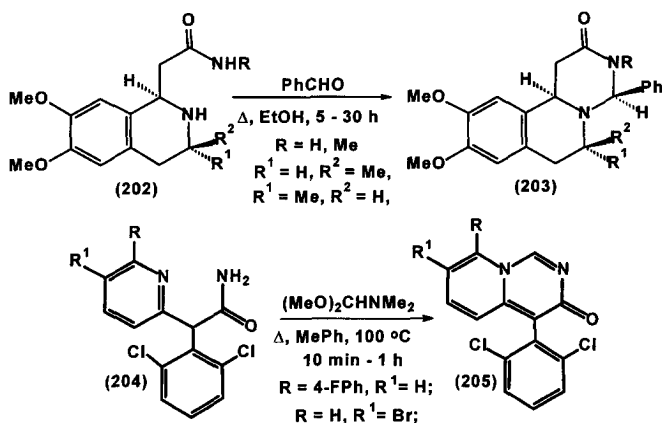
Cyclocondensation of  $\alpha$ -aryl-2-pyridylacetamides and 2-(3,4-dihydroisoquinolin-1-yl)acetamide with  $\text{Et}_2\text{CO}_3$  in the presence of  $\text{NaOEt}$  in boiling  $\text{EtOH}$  afforded 4-aryl-2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones (99JHC389) and 6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione (98MIP15), respectively.



Treatment of resin-bound iminophosphorane **197** with an excess of solid CO<sub>2</sub> and CS<sub>2</sub> in a sealed glass tube, and with aryl isocyanates afforded 1-oxo-, 1-thioxo- **198**, and 1-arylimino-1*H*-pyrido[1,2-*c*]pyrimidine-3-carboxylates **199** (01JMC1011). Reaction of iminophosphorane **200**, derived from 2-(2-azidophenyl)pyridine with excess PPh<sub>3</sub>, yielded 6*H*-pyrido[1,2-*c*]quinazoline-6-thione (**201**).

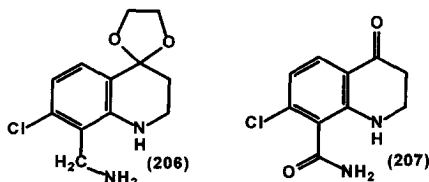
6,6-Dimethyl-6,7-dihydropyrido[1,2-*c*]quinazolinium salt (**142**) was obtained in the reaction of 2-(2-aminophenyl)pyridine and acetone (97AJC109).

Reactions of 3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamides **202** (R = H) with 36% aqueous CH<sub>2</sub>O at 60 °C gave 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones **152** and their 3-methyl derivatives (97LA1165). When the reaction was carried out in the presence of 37% aqueous NaOH 3-hydroxymethyl derivatives **151** were obtained. Reactions with PhCHO were stereospecific to afford only diastereomers **203**.



Reaction of 2-pyridineacetamides **204** with DMF dimethylacetal afforded 3*H*-pyrido[1,2-*c*]pyrimidin-3-ones **205** (98MIP11, 00USP6147080).

3-Phenyl-5,6-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]quinazoline-7-one and 1,7-dione **179** (X = H<sub>2</sub> and O) were prepared from tetrahydroquinolines **206** and **207** with *N*-(ethoxycarbonyl)thiobenzamide and PhCOCl, respectively (98EJM763).

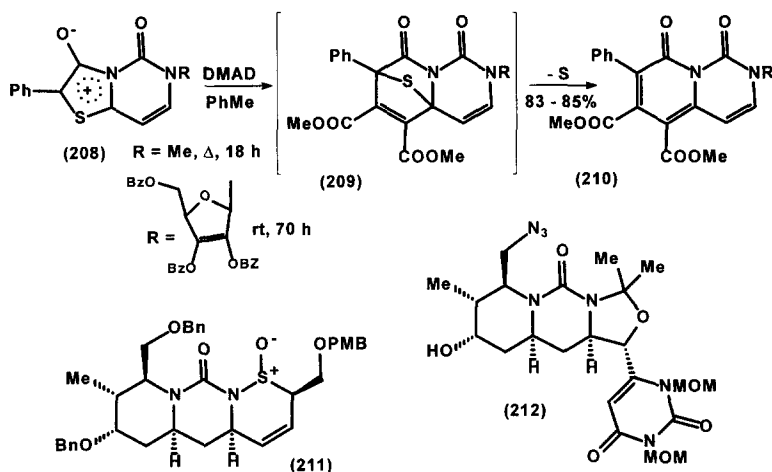


5. *By Formation of Two Bonds from [4+2] Atom Fragments*

8,9-Difluoro-5-methyl-6,7-dihydro-5*H*-pyrido[3,2,1-*ij*]quinazoline-1,3-dione was obtained when methyl 5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline-8-carboxylate was treated dropwise with  $\text{ClSO}_2\text{NCO}$  in  $\text{CH}_2\text{Cl}_2$  at  $-20^\circ\text{C}$ , then the reaction mixture was treated with  $\text{AcONa}$ , and after the removal of the solvent *in vacuo* the residue was treated portionwise with  $\text{NaOt-Bu}$  at  $5^\circ\text{C}$  in THF (01MIP23).

6. *Ring Transformation*

1,3-Dipolar cycloaddition reaction of thioisomünchnones **208** with dimethyl acetylenedicarboxylate (DMAD) furnished adducts **209**, which underwent a sulfur extrusion to give 2-substituted-7-phenyl-1,8-dioxo-1*H*,8*H*-pyrido[1,2-*c*]pyrimidine-5,6-dicarboxylates **210** (00OL581).

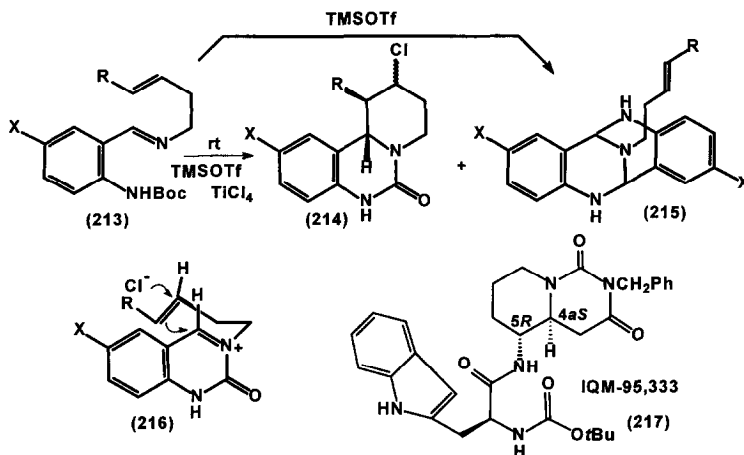


Stereospecific ring-opening and [2,3]-sigmatropic rearrangement of tricyclic **211** yielded perhydropyrido[1,2-*c*]pyrimidin-1-one **149**, having all six of the stereogenic centers of 7-epicylindrospermopsin in place. Treatment of **212** with 1 N HCl in THF at  $85^\circ\text{C}$  gave **157** (01JA8851).

7. *Miscellaneous*

Tetracyclic derivatives **215** formed exclusively from imines **213** on the action of  $\text{TMSOTf}$ , whereas in the presence of  $\text{TiCl}_4$  both 1*H*-pyrido[1,2-*c*]quinazolin-6-ones **214**, as a  $>9:1$  mixture of  $\alpha/\beta$  chloro epimers, and tetracyclic derivatives **215** were obtained. Imine **213** (R = H) gave a 3:1

mixture of  $\alpha/\beta$  chloro epimers of **214** ( $R = H$ ) in 47% yield when a mixture of Lewis acids,  $TiCl_4$  and  $Ti(OiPr)_4$  was used. The stereoselectivity of the formation of **214** is rationalized by a chair-like transition state **216** with equatorial attack of chloride ion (98TL7239, 00JOC655).



#### D. APPLICATIONS AND IMPORTANT COMPOUNDS

Perhydropyrido[1,2-*c*]pyrimidin-1,3-ones were applied in the total synthesis of cyanobacterial hepatotoxin 7-epicylindrospermopsin (01JA8851).

(4*aS*,5*R*)-2-Benzyl-5- $\{N-[(tert\text{-}butoxycarbonyl)\text{-}L\text{-}tryptophyl]amino\}$ perhydropyrido[1,2-*c*]pyrimidine-1,3-dione (**217**) (97BJP759) and its 2-substituted congeners (01JMC2219) are potent and selective CCK-A receptor antagonists both *in vitro* and *in vivo* with an anxiolytic-like activity. They exhibit nanomolar CCK-A receptor affinity and higher than 8000-fold potency at the CCK-A than at the CCK-B receptor. The other stereoisomers are less potent and selective CCK-A antagonists than **217** (97JMC3402). Ethyl 1-(arylimino)-1*H*-pyrido[1,2-*c*]pyrimidine-3-carboxylates exhibited anti-inflammatory activities in carrageenan mouse paw edema model (01JMC1011).

Among other drugs, clearance (96MI25, 99JPP905) and absolute oral bioavailability (00MI48) of actisomide (**2**) were predicted in humans from animal data by different methods. Biological activities and phosphodiesterase activity of **3** were investigated on different biochemical assays (97BJP743, 97MI56, 98LS265, 98LS953, 98MI4, 98MI62, 98MI92, 99JBC4839, 99MI20, 99MI21, 00JBC30069, 00MI49, 00MI50, 00MI51).

Trequinsin (**3**) is a potent inhibitor of T6PDE2A enzyme belonging to class I phosphodiesterases (01JBC11559). Trequinsin was determined in biological fluids by using labeled 2,3-benzodiazepine derivatives (97MIP13). Trequinsin was patented as a component of a synergistic analgesic composition (00MIP2). Among other PDE4 inhibitors, **3** was also claimed for treating chronic obstructive pulmonary disease (00MIP17), obesity (01MIP9), illness of the bladder (01GEP19935209), erectile dysfunction (00USP6156753, 01MIP21), and treating exercise-, air- and pollution-induced asthma (00MIP18).

2-Arylimino-2,3,6,7-tetrahydro- (00MIP19) and 2-aryloxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (00MIP20) were patented as PDE inhibitors and as useful agents for treatment of respiratory disorders, respectively.

Hydrazone of 1-hydrazino-1-hydroxy-4-phenyl-1,2-dihydro-3*H*-pyrido [1,2-*c*]pyrimidin-3-one was patented as cross-linkers for making physiologically compatible and H<sub>2</sub>O insoluble hydrazine or hydrazono compounds (97JAP(K)97/59303).

## VII. Pyrido[2,1-*c*][1,4]oxazines and Their Benzo Derivatives

### A. STRUCTURE

#### 1. Thermodynamic Aspects

Acid–base property of ofloxacin (**5**) was studied in H<sub>2</sub>O–MeCN mixtures (97ACS896, 97TAL1271, 98JC(A)411, 98MI40). Factor analysis was applied to find correlation between acidic constants of **5** in H<sub>2</sub>O–MeCN mixtures (97MI44). An excellent correlation was found between the logarithm of the dissociation constant value ( $pK_{a_1}$ ) of **5** in the binary mixtures and their corresponding solvatochromic parameter of polarity–polarizability ( $\pi^*$ ) and the hydrogen bond basicity  $\beta$  solvatochromic parameter (97MI44). Macroscopic dissociation constants of **5** were reported [ $pK_{a_1}$  5.97;  $pK_{a_2}$  8.28 (97MI32),  $pK_{a_1}$  6.05,  $pK_{a_2}$  8.22 (98JPS215), and  $pK_{a_1}$  6.10,  $pK_{a_2}$  8.28 (00MI44)].  $pK_a$  values of quinoline-3-carboxylic acids, including **5**, were determined by electrophoretic, chromatographic, potentiometric, and absorptiometric methods in H<sub>2</sub>O–MeCN mixtures (01MI2). The effect of surfactants on equilibria in the Al(III)-ofloxacin (98MI79, 01BCJ1261), and adsorption of **5** on aluminumoxide (01BCJ1261) were studied.

Apparent partition coefficient ( $\log D$ ) at an ionic strength of  $I=0.02$  M,  $\log P$  value of the neutral microspecies and the acidic dissociation constant of **5** was calculated (97ANC4143). The distribution coefficient of **5** was determined between 1-octanol and universal buffer in the pH range 3–10 at a

constant ionic strength of 0.3 (97MI15). The apparent partition coefficient of **5** ( $-0.47 \pm 0.02$ ) and levofloxacin (**6**) ( $-0.42 \pm 0.03$ ) was determined in 1-octanol-H<sub>2</sub>O system at physiological pH (7.4) at 25 °C (98JPS215). That of **6**, its 10-amino derivatives (00AAC2126), and (3*S*,3'*S*)-10-(3'-aminopyrrolidin-1-yl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids (98CPB1710) was determined in a CHCl<sub>3</sub>-0.1 M phosphate buffer (pH 7.4).

Dissolution of **5** could be enhanced in H<sub>2</sub>O by solid dispersion systems with urea and mannitol (97MI27). A method for solubilizing **5** and **6** at near physiological pH was patented (98EUP856316). Solubility characteristics of **5** was investigated in an *in vitro* tear model (98MI24).

Human intestinal absorption of **5** (01JPS749) and **6** (01MI30) was predicted by using five Abraham descriptors and CaCo-2 monolayer, respectively. The effect of hydrophobicity and molecular mass on the accumulation of 10 fluoroquinolones, including **5**, by *Staphylococcus aureus* were evaluated (01MI14).

Related substances were quantitatively determined in injection formulation of **5** by TLC (98MI14). Ofloxacin (**5**) and enoxacin was simultaneously determined in body fluid by a TLC-fluorescence spectrodensitometry method (98MI100). Ofloxacin was determined and identified in various biological fluids (97JC(B)147, 97MI13, 97MI38, 97MI50, 98JC(A)343, 98JC(B)97, 98MI51, 01JC(B)91, 01JC(B)311, 01YZ319), in a mixture of fluoroquinolones (97MI26, 00MI18), in bulk (00MI77), and in different pharmaceutical formulations (96MI18, 97MI45, 98MI6, 98MI32, 98MI35, 98MI36, 98MI42, 98MI53, 98MI65, 98MI87, 98MI102, 99JLC2225, 99MI10, 99MI13, 00MI4, 00MI5, 00MI20, 00MI68) and in meats as residual (98MI56) by different HPLC methods. Selection of a mobile phase in HPLC was reported (00MI8). A multi-residue methodology was developed and validated to determine **5** in foods (98MI101). An electrogenerated chemiluminescence HPLC was developed for determination of **5** residue in chicken tissues using tris(2,2'-bipyridinyl)-Rh(II) (99MI6). An HPLC method with fluorescence detection was developed for determination of **5** and **6** in urban waste water (01ANC3632). Rule of intersection point of retention for **5** in bonded-phase chromatography with ion suppression was studied (98MI15). A study was reported on the solid surface room temperature phosphorimetry or delayed fluorescence of seven quinolones, including **5** (00MI75).

Plasma protein binding of **5** was determined by ultrafiltration method (98JPS215, 98MI91). The binding characteristics of **5** with catalase were studied by fluorescence spectroscopy in aqueous solution (01MI29). The binding of **6** to clay minerals was investigated (97MI60). The electrochemical behavior of **5** at Pt/GC ion implantation modified electrode was studied by voltammetry (01MI18).

Ofloxacin (**5**) was determined, sometimes besides other drugs in biological fluids, in drug substance, and in different pharmaceutical formulations by alternating current oscillopolarographic titration (98MI9, 98MI95), by conductimetric titration (99MI32), by Kalman filter spectroscopy (98MI66), by different spectrophotometric methods (96MI17, 96TAL2123, 97MI7, 97MI14, 97MI16, 97MI39, 97MI46, 97MI48, 97MI62, 98MI8, 98MI27, 98MI31, 98MI46, 98MI54, 98MI60, 98MI90, 99MI35, 00MI21, 00MI27, 00MI30, 00MI32, 00MI33, 00MI36, 01MI1, 01MI22, 01MI35), by dual-wavelength spectrometry (00MI61), by fluorospectrophotometry (97MI29, 97MI32, 97MI34, 98JAP(K)98/258059, 98MI43, 00MI16, 00MI27, 00MI59, 01MI6), by synchronous-derivative fluorometry (01MI34), by single-sweep oscillopolarography (00MI69), by flow-injection chemiluminescence (00MI10, 00MI17), by polarography (96MI23, 97MI57, 98TAL83), by capillary electrophoresis (99JLC281, 00MI2, 00JC(B)255), by high performance electrophoresis (97MI42, 98MI59, 98MI80), by capillary zone electrophoresis (96MI6, 99MI16, 00MI60), by linear sweep voltammetry (96MI13), by a TLC (00MI9), by a HPTLC (99MI57), and by a LC/MS/MS (97ANC4143) methods, furthermore with chloranil charge-transfer reaction (99MI61). Capillary zone electrophoresis and capillary electrokinetic chromatography were applied for analysis of **5** and its major degradation products (99JC(A)253). A fluorometric determination and a quantitative device for **5** in eye tissues was developed (98JAP(K)98/258059). The average recovery of **5** from suppositories was 101.7% with RSD of 1.36% (00MI14). Ofloxacin liposomes were prepared by a pH-gradient method and the encapsulation efficiency was determined by UV after separation of **5** (00MI78). Capillary electrophoretic separation of **5** was optimized (97JC(A)215). A chemiluminescence method using tris(2,2'-bipyridyl)ruthenium(II) and Ce(IV) in H<sub>2</sub>SO<sub>4</sub> medium was developed for the determination of **5** (01TAL885). Micellar and microemulsion electrokinetic chromatographic separation of six quinoline-3-carboxylic acids, including **5** was studied (01MI3). A quantitative analytical method for filter-optic chemical sensors based on fluorescence quenching for determination of **5** was developed (01MI4). Theophylline was determined in serum with concomitant application of **5** by dual-wavelength spectrophotometry (01MI20). The mechanism of interaction between **5** and bovine serum albumin on each other in aqueous solution was investigated by using fluorescence spectra and microcalorimetry (00MI74).

The photolysis of **5** was investigated in neutral aqueous solution by ESR spectroscopy (98CPB1021).

Levofloxacin (**6**), (98MI58), and DV-7751a (**218**) (97MI40) was determined in biological media and formulated products by HPLC (97AAC2196, 97MI37, 97MI51, 97MI52, 98MI48, 98MI97, 00MI42,



00MI57, 00MI58, 01MI17, 01MI36), by UV spectrophotometry (98MI19, 00MI3), by spectrofluorimetry (00MI1, 00TAL1149), and by micellar electrokinetic capillary chromatography (99MI59). A sensitive and selective erbium-sensitized luminescence method was developed for determination of **6** in tablets and human urine and serum (00MI40). Nine analytical methods for determination of **5** and **6** were summarized (99MI54).

A stereoselective determination of enantiomers of **5**, its *N*-oxide and *N*-desmethyl metabolites in human urine was developed by capillary electrophoresis using laser-induced fluorescence detection and sulfonated  $\beta$ -cyclodextrin in the running buffer (01JC(B)169).

The enantiomers of **5** (97JC(A)235, 97MI10, 97MI24, 97MI33, 97MI49, 97MI53, 97MI61, 98JC(A)153, 98JPS960, 98MI38, 98MI74, 98MI77, 99MI31, 99MI33, 99MI34, 00JC(A)295, 00MI25, 00MI63, 01MI26), its *N*-ethyl and 9-chloro derivatives (00JC(A)295) and 10-(8-amino-6-azaspiro[3,4]octan-6-yl)-2,3-dihydro-9-fluoro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (97JC(A)235) were resolved by capillary electrophoresis. Optical resolution of **5** by electrokinetic chromatography was patented (97JAP(K)97/236581) and published (01MI19). Separation of enantiomers of **5** was also achieved by HPLC on a chiral column (98MI82, 98MI86, 00JAP(K)00/302698, 00MI43), and by using chiral ligand (99JC(B)151). Enantiomers of **5** were separated on TLC containing 3,5-dinitrobenzoyl substituted  $\beta$ -cyclodextrin bounded stationary phase (00MI34). Determination of the enantiomers of **5** was carried out by synchronous-first order derivative of fluorometry (00MI22, 00TAL359).

A computer program was compiled to work out the ray-tracing of UV detector of high performance capillary electrophoresis at the investigation of **5** and **6** (98MI59). The capacity factor of **5** at different temperature and at different mobile phase compositions was experimentally determined in bonded-phase chromatography with ion suppression (98MI15).

Complex formations of **5** with Cu(II) (96TAL2123), Al(III) (99MI17, 99MI18), Mg(II) (98MI10, 99MI18), Ca(II) (99MI18), Tb(III) (96MI11), La(III), Pr(III), Nd(III), and Sm(III) (96MI19) were investigated. Complex formation constants between **5** and some divalent cations were measured at pH 7.5 (00MI44). A colorimetric method was developed for determination of Fe(III) with **5** (00MI73). Interfacial phenomena involving Fe(III) ofloxacin complexes at the H<sub>2</sub>O-1,2-dichloroethane interface was investigated (99MI14, 01MI28). Simultaneous determination of Pr, Nd, Ho, and Er in rare earth mixtures was developed based on the absorption spectra of 4*f*-electron transitions of Pr, Nd, Ho, and Er complexes with **5** (00MI41). The complexation equilibrium between **5** with tungstate, molybdate and vanadate was studied by conductometric, potentiometric and spectrophotometric methods (01MI37). Luminescence properties of Tb(III) and

Eu(III) complexes of quinolinecarboxylic acids, including **5**, were studied (00MI31). Those of complexes of **5** with Eu(III) and Tb(III) ion were studied, and they were applied for analysis of **5** in medicinal preparations (00UKZ115). Stability of lanthanide complexes with **5** was studied (00MI67). The fluorescence spectra of **5** complexed with Co(II) and ATP was measured (01SA(A)1317).

Thermal stability and decomposition of **5** were investigated by using TG and DSC (00MI46). Stability of 1% injection of **5** (97MI4) and that of a nasal spray, containing **5** and ephedrin HCl (98MI60) were studied by UV spectrophotometry. Physical compatibility and chemical stability of linezolid admixed with **5** and **6** were measured for 7 days at 4 and 25 °C (00MI66). The solid surface room temperature phosphorimetry and the solid surface delayed fluorescence of **5** was first established with filter paper as a solid substrate (00MI75).

Assay and analysis of pazufloxacin (**8**) and its related substances were established by HPLC (98MI89).

## 2. Theoretical Calculations

A quantitative structure–retention relationship was developed for the retention behaviors and molecular descriptors of different antimicrobial quinolones, including **5**, in PRP-1 column using molecular mechanisms (MM<sup>+</sup>) and AM1 semiempirical methods (98MI26). The combination of molecular topological methods, using 137 quinolones, including **5**, provided an excellent tool for design of new antibacterial quinolones (00AAC2764). A non-linear neural network model to perform cluster analysis was developed and its applications was presented in the field of antibacterial quinolones, including **5**, too (96MI15). A series of 18 antibacterial quinolones, including **5**, was applied in a QSAR study based on a modified electrospatial state index (97MI5). A series of compounds, including **5**, was used in a molecular connectivity approach for designing new antimicrobial compounds (97MI31). Structure–activity relation of 20 fluoroquinolones, including **5**, was studied using *Escherichia coli* (98MI22). Molecular topology has been applied to find new lead antibacterial compounds. Ofloxacin (**5**) was included in the training group (00BMCL2033). Anti-HIV effects of 101 6-fluoro- and 6-desfluoroquinolones, including 3-methyl- and 3-fluoro-methyl-10-[4-(2-pyrimidinyl)piperazin-1-yl]-7-oxo-2,3-dihydro-7*H*-pyrido [1,2,3-*de*]-1,4-benzoxazines, were investigated by a QSAR analysis, which takes into account the solvation effect and the 3D characterization by the VULSURE/GRD program (01MI15). Blood–brain barrier permeation of **5** and **6**, among other drugs, was predicted from their three-dimensional molecular structure by a computational method (00JMC2204).

2-(2-Imidazolynyl) derivative of 8-methyl-2,3,6,7-tetrahydro-5*H*- and 8-methyl-7-methoxy-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines were included in a 3D-QSAR CoMFA study on imidazolinergic I<sub>2</sub> ligands (00JMC1109).

The asymmetric synthesis of (4*R*,9*S*,9*aR*)-4-phenyl-1-trimethylsilyloxy-9-vinylperhydropyrido[2,1-*c*][1,4]oxazine by a high level of stereoselectivity in the cyclization of (3*R*,5*R*)-5-phenyl-3-phenylsulfanyl-4-(6-trimethylsilylhex-4-enyl)-2-trimethylsilyloxymorpholine was rationalized via AM1 calculations (98T10309).

### 3. UV, Fluorescence and IR Spectroscopy

Spectroscopic properties of **5** were studied (00MI11). Spectral characteristics of **5** of 0.1 N NaOH solution were investigated by UV spectroscopy (97MI17). Three dimensional fluorescent spectral characteristics of fluoroquinolones, including **5**, were studied in varying media (00SA(A)1787). The structure of **8** was confirmed by UV and IR studies (98MI89).

### 4. NMR Spectroscopy

<sup>1</sup>H and <sup>19</sup>F NMR assay was developed for quantitative determination of **5** and other fluoroquinolones in formulations (95MI2). <sup>1</sup>H and <sup>13</sup>C NMR, HMQC and HMBC spectra of **5** hydrochloride were measured and analyzed (99MI26). 9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-7-one, a decarboxylated product of **5** was characterized by UV, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (97MI18).

The complexation of **6**, ciprofloxacin, and lomefloxacin with metals ions were studied in aqueous solution (pD 2.5; 37 °C) by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (99MI18). Titration experiments have revealed that the binding ability of **6** towards Al<sup>3+</sup> ion is much stronger than that of ciprofloxacin and lomefloxacin. Other metal ions (Ca<sup>2+</sup> and Mg<sup>2+</sup>) formed much weaker complexes.

The chemical structure of **8** was confirmed by NMR studies (98MI89).

### 5. Mass Spectrometry

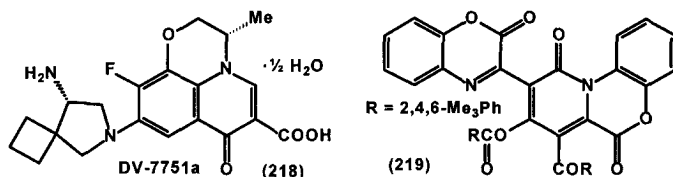
An on-line chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (LC-APCI/MS/MS) methods was developed for rapid screen of pharmacokinetics of different drugs, including **5** (98RCM1216). The electron impact mass spectrum of **5** and ethyl 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate was reported (97MI28). Electron impact/Fourier transform

ion cyclotron resonance mass spectrometry was used to study the mass spectra of **5** (96MI20).

The chemical structure of **8** was also confirmed by mass spectrometry studies (98MI89).

## 6. X-ray Investigation

X-ray investigation of (4*R*,8*aR*)-*trans*-4*H*,9*aH*-4-phenyl-9-vinylideneperhydropyrido[2,1-*c*][1,4]oxazin-1-one justified a *cis* relationship between 9*a*-H and the phenyl group at position 4, thus establishing an (*R*) absolute configuration at the ring junction (98EJOC2461). The stereostructure of *cis*-4,9*a*-H-4-phenyl- (00JOC3771), 4*β*,6*β*,8*β*,9*αα*-H-6-ethyl-8-methyl-4-phenyl- and 4*β*,6*β*,8*β*,9*αα*-H-8-hydroxy-4-phenyl-6-propylperhydropyrido[2,1-*c*][1,4]oxazin-1-ones (00JOC4435) were determined by X-ray diffraction experiments.



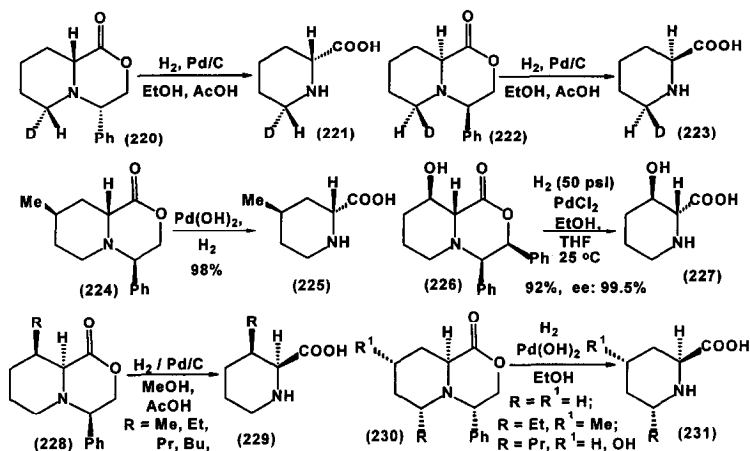
The solid state structure of (3*S*,8'*S*)-10-(8-amino-6-azaspiro[3,4]octan-6-yl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**218**) was determined by X-ray diffraction study (98CPB1710). The structure of 6,10-dihydropyrido[2,1-*c*][1,4]benzoxazine-6,10-dione **219** was established by X-ray diffraction analysis. It contains a crystal solvate with *p*-xylene (99MI40).

## B. REACTIVITY

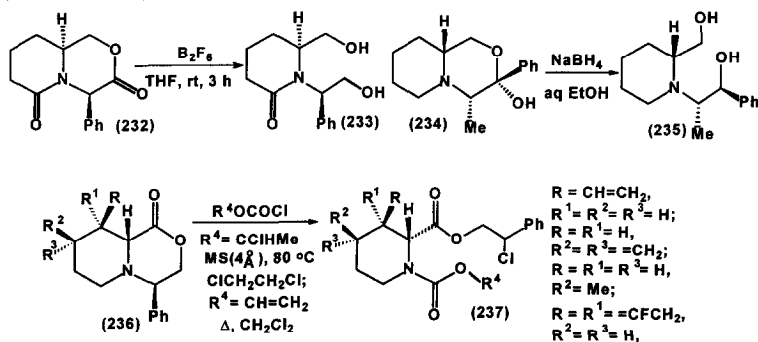
### 1. Ring Opening

Catalytic hydrogenation of perhydropyrido[2,1-*c*][1,4]oxazin-1-ones **220** and **222** yielded the enantiomers D-[6(*R*)-D]- and L-[6(*S*)-D]-pipecolic acids (**221** and **223**) in greater than 95% enantiomer excess (97JA6446). (2*R*,4*R*)-4-Methylpipecolic acid (**225**) and (2*R*,3*R*)-3-hydroxypipecolic acid (**227**) were obtained by hydrogenation of perhydropyrido[2,1-*c*][1,4]oxazin-1-ones **224** and **226** over Pearlman's catalyst and PdCl<sub>2</sub>, respectively (97SL799, 98TL3659). Similarly, pipecolic acids **229** and **231** were prepared from **228** (99TL3699) and **230** (00JOC4435, 00SC2565). Catalytic hydrogenation of the appropriate 4-phenyl-9-(2-propoxycarbonylamino)perhydropyrido

[2,1-*c*][1,4]oxazin-1-one in 90% EtOH in the presence of 20% Pd(OH)<sub>2</sub>/C catalyst under 45 psi hydrogen gave (2*R*,3*S*)-3-(2-propoxycarbonylamino)-pipercolinic acid (98MIP12). Similarly, optically active 4- and 5-substituted pipercolic acids were prepared from 4-phenyl-7- and -8-substituted perhydropyrido[2,1-*c*][1,4]oxazin-1-ones by catalytic hydrogenation over Pearlman's catalyst (01EJOC2385, 00TA3913).

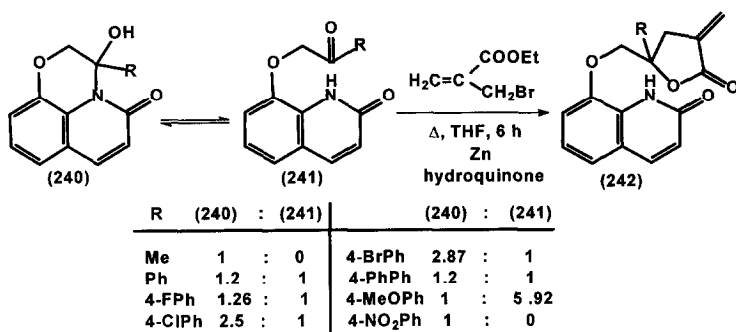


Treatment of perhydropyrido[2,1-*c*][1,4]oxazine-3,6-dione **232** with B<sub>2</sub>H<sub>6</sub> yielded (–)-(2*R*)-[(2*S*)-hydroxymethyl]piperidin-1-yl]-2-phenylethanol (**233**) (00T233). Reduction of (±)-(3*R*,4*R*,9*aS*)-4-methyl-3-phenylperhydropyrido[2,1-*c*][1,4]oxazin-3-ol (**234**) with NaBH<sub>4</sub> yielded ring-opened product **235** (97JHC1813).

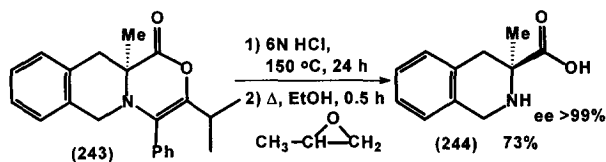


Treatment of perhydropyrido[2,1-*c*][1,4]oxazin-1-ones **236** with vinyl and 1-chloroethyl chloroformate in the presence of 4Å molecular sieves afforded ring-opened (2*R*)-pipecolic acid derivatives **237** (97SL799, 98EJOC2461, 98T10309). Similarly, perhydropyrido[1,2-*c*][1,4]oxazin-1-one **238** yielded (2*S*)-pipecolic acid derivative **239** (98T10309).

Reaction of 2,3-dihydro-3-hydroxy-3-methyl- **240** (R = Me), or a mixture of 2,3-dihydro-3-hydroxy-3-aryl-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-ones **240** (R = Ar) and (8-arylmethoxy)quinolin-2(1*H*)-ones **241** (R = Ar) with ethyl 2-(bromomethyl)acrylate in the presence of activated Zn and hydroquinone gave 8-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-furanyl)-methoxy]quinolin-2(1*H*)-ones (**242**) (97HCA1161). 6,7-Dihydro derivatives of **240** reacted similarly (00HCA349).



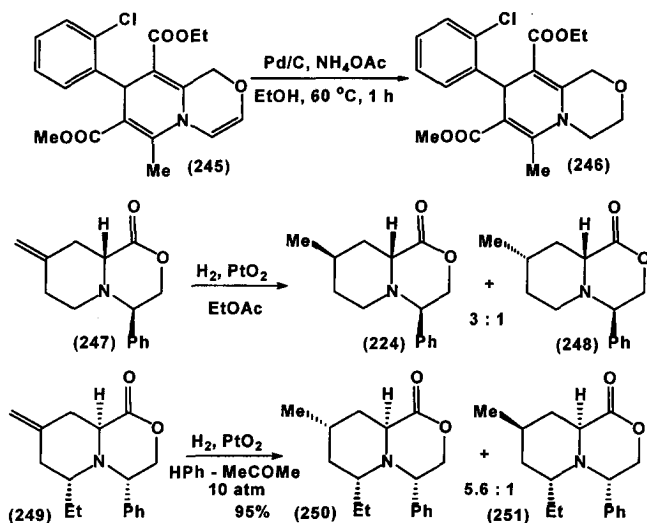
Treatment of (11*aS*)-3-isopropyl-11*a*-methyl-4-phenyl-1,6,11,11*a*-tetrahydro[1,4]oxazino[4,3-*b*]isoquinolin-1-one (**243**) with 6 N HCl in a pressure tube, then the reaction of the work-up residue with propylene oxide gave (3*S*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**244**) (99S704).



Treatment of 8-fluoro-1,2-dihydro-4*H*,6*H*-[1,4]oxazino[4,3-*a*]quinoline-4,6-dione with 6 N aqueous NaOH and PhCH<sub>2</sub>Br under reflux overnight and with NaOMe in DMF at ambient temperature yielded 1-(2-benzyloxyethyl)- and 1-vinyl-6-fluoro-1,4-dihydroquinoline-2-carboxylic acids, respectively (01SL833).

## 2. Reduction, Hydrogenation

Reduction of a perhydropyrido[1,2-*c*][1,4]oxazin-1-one with  $\text{BH}_3$  in anhydrous THF at room temperature yielded a perhydropyrido[1,2-*c*][1,4]oxazine (00MIP1).



1,3,4,8-Tetrahydropyrido[2,1-*c*][1,4]oxazine-7,9-dicarboxylate **246** was obtained from 1,8-dihydro derivative **245** over Pd/C catalyst in the presence of  $\text{NH}_4\text{OAc}$  (97CP2188071). Catalytic hydrogenation of an epimeric mixture of (4*S*,9*aS*)-1-trimethylsilyloxy-4-phenyl-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*c*][1,4]oxazine over Raney Ni afforded perhydro derivatives (00SC2565). Catalytic hydrogenation of 4-phenyl-8-methyleneperhydropyrido[2,1-*c*][1,4]oxazin-1-ones **247** (97SL799, 01EJOC2385) and **249** (00JOC4435) afforded epimeric mixtures of 8-methyl-4-phenylperhydropyrido[2,1-*c*][1,4]oxazin-1-ones **224**, **248** and **250**, **251**, respectively. Reduction of 4*β*,9*αα*-H-4-phenylperhydro[2,1-*c*][1,4]oxazin-1,8-diones with K-Selectride in THF at  $-78^\circ\text{C}$  afforded 4*β*,8*β*9*αα*-H-8-hydroxy derivative (00JOC4435, 01EJOC2385). When  $\text{BH}_3$ -THF was used as reducing agent in THF at  $-60^\circ\text{C}$  4*β*,8*α*9*αα*-H-8-hydroxy epimer was obtained (01EJOC2385).

Reduction of 8-nitro-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinolin-4-one with  $\text{BH}_3$  in THF afforded 8-nitro-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinoline (97MIP4). Then the nitro group was reduced by catalytic hydrogenation over 5% Pd/C catalyst in acidified MeOH to yield 8-amino derivative. Catalytic hydrogenation of 3-nitro-6,6*a*,7,

8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine over 10% Pd/C in an 1:1 mixture of EtOH and EtOAc gave an 3-amino derivative (01MIP1). Nitro group, either in position 8 of (3*S*)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, or in the substituent attached to the position 10 of this tricyclic ring system was catalytically hydrogenated to an amino group over 10% Pd/C catalyst (99MI56). 9-Amino-2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine was obtained by reduction of the 5-oxo derivative with Red-Al in THF at 5–10 °C (99GEP19802239). 8-Amino derivative was obtained by reduction of 8-nitro-10-(2,6-dimethyl-4-pyridyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-carboxylate (00MI37).

A side-chain COOH group in 5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one was reduced into a HOCH<sub>2</sub> group with NaBH<sub>4</sub> in a 1:1 mixture of MeOH and THF at 5 °C (98MIP13). Ethyl 7-oxo-2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-2-carboxylate was prepared by the catalytic hydrogenation of the 7-oxo-5*H* derivative over 10% Pd/C catalysts in EtOH (99EUP894796).

Catalytic hydrogenation of 9-(3-hydroxy-1-propynyl)-*N*-(4-chlorobenzyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxamide over 5% Pd/C in a 1:1 mixture of THF and MeOH afforded a mixture of 9-propyl and 9-(3-hydroxypropyl) derivatives (01MIP2).

Some further reductions and hydrogenations leading to ring-opened products are mentioned in Sections VII.B.1 and VII.B.5.

### 3. Oxidation

Swern oxidation of perhydropyrido[2,1-*c*][1,4]oxazin-1-oles using oxalyl chloride (97SL799, 98EJOC2461, 98T10309, 00JOC4435, 00SC2565, 01EJOC2385) or COCl<sub>2</sub> (99SL1094) in the presence of NEt<sub>3</sub> in DMSO gave perhydropyrido[2,1-*c*]oxazin-1-ones.

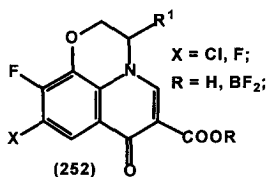
Treatment of an epimeric mixture of 1-hydroxy-8-methylene-4-phenyl-perhydropyrido[2,1-*c*][1,4]oxazines with 4% aqueous solution of OsO<sub>4</sub> in aqueous THF in the presence of NaIO<sub>4</sub> at room temperature gave an epimeric mixture of 1-hydroxyl-8-oxo derivatives (00JOC4435, 01EJOC2385).

Treatment of ethyl 10-methylthio-9-fluoro-3-methyl-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate with oxone in aqueous MeOH at 0 °C afforded 10-methylsulfonyl derivative (99H(51)1563). Methylthio group in a 7-(4-methylthiophenyl)-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-carboxamide was oxidized to a sulfoxide and a sulfone group (00MIP1).



#### 4. Reactivity of Ring Carbon Atoms

The fluoro atom at position 10 in 9,10-difluoro- and 10-fluoro-9-chloro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids (**252**, R = H) (96MIP1,P2, 97USP5677456, 98GEP19652219, 98MI39, 98MIP5,P14,P19, 98MI37, 98USP5854227, 99BMCL3063, 99H(51)1563, 99JAP(K)99/147883, 99MI23, 99MI36, 99MI56, 99MI58, 99MIP2,P7, 00USP6121285) and in their 6-[(difluoroboryl)oxycarbonyl] derivatives (**252**, R = BF<sub>2</sub>) (97MIP5,P10, 98CPB1710, 98JAP(K)98/130149,P(K)98/287669, 98MIP5,P9,P17, 99JAP(K)99/12278, 99MIP4,P7, 00AAC2126, 00MIP12, 00USP6121285, 01MIP10,P17) was substituted with different cyclic amines. The substitution of 10-fluoro atom with 1-methylpiperazine in boiling MeCN was enhanced by using basic Al<sub>2</sub>O<sub>3</sub> (activated basic, Brockman I) or strongly basic Amberlite IRA-900 ion-exchange resin (96MI10). The substitution of 10-fluoro atom with (3*S*)-(tert-butoxycarbonylamino)pyrrolidine in boiling MeCN was carried out in the presence of DBU (96MI12). Reaction of 9,10-difluoro- and 9-fluoro-10-chloro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids and their boron complexes with 1-methylpiperazine and piperazine were studied in detail (98H(48)1111).



Reaction of 9,10-difluoro-3-methyl-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**252** X = F, R = H, R<sup>1</sup> = Me) with 8 M aqueous solution of KOH under reflux for 6 h, and in the presence of an alcohol or phenol afforded 10-hydroxy, 10-alkoxy and 10-aryloxy derivatives, respectively (96JAP(K)96/291144, 99MI5).

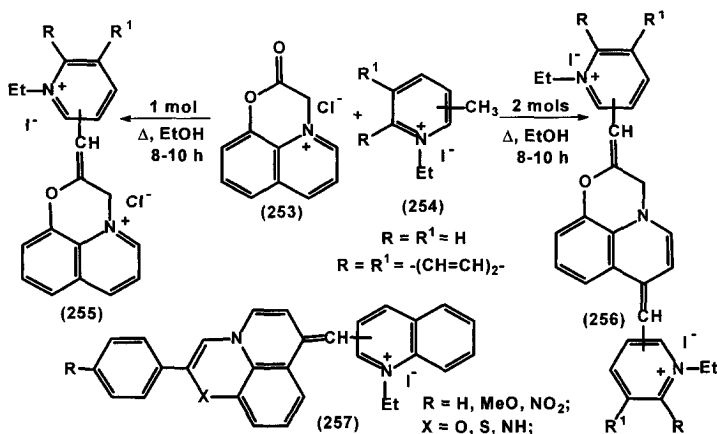
10-Methylsulfonyl-9-(4-methylpiperazinyl)-3-methyl-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was obtained from 9-fluoro-10-methylsulfonyl derivative with 1-methylpiperazine in MeCN at 60 °C for 16 h. The boron chelate of 10-methoxysulfonyl-9-fluoro derivatives gave the same result (99H(51)1563).

Reaction of *N*-(4-chlorobenzyl)-9-iodo-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxamide and HC≡CCH<sub>2</sub>OH in the presence of Cu(I)I and (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> in Et<sub>2</sub>NH under argon atmosphere for 18 h gave 9-(3-hydroxy-1-propynyl) derivative (01MIP2).

7-Hydroxy group of 7-hydroxy-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid esters and 6-carboxamides was changed for a chloro atom by treatment with  $\text{PPh}_3$  and  $\text{CCl}_4$ , and the 7-chloro atom was changed for different aryl groups in the presence of  $(\text{Ph}_3\text{P})_4\text{Pd}$  catalyst (00MIP3). Bromo atom of ethyl (3*S*)-10-bromo-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate was changed for a hetaryl group with tributyl stannyl derivatives of hetaryl bicycles in the presence of  $(\text{Ph}_3\text{P})_2\text{Pd}(\text{II})\text{Cl}_2$  in boiling toluene (00MIP10).

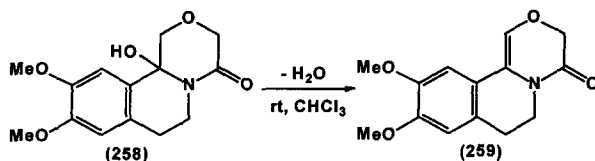
9,10-Difluoro-3-methyl-8-nitro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was obtained from 8-unsubstituted derivative by treatment with  $\text{KNO}_3$  (99MI56).

Reaction of 2-oxo-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzoxazinium chloride (253) with 1 and 2 mol of the appropriate heterocyclic quaternary salt 254 in the presence of a few drops of piperidine gave mono and bis condensation products 255 and 256, respectively (98MI45). Similar reactions of 2-arylpyrido[1,2,3-*de*]-1,4-benzoxazinium bromides and 254 [ $\text{R} = \text{R}' = -(\text{CH}=\text{CH})_2-$ ] yielded condensation products 257 ( $\text{X} = \text{O}$ ).



Michael addition of dialkyl cuprate reagents to optically active 4-phenyl-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazin-1-one afforded stereoselectively 9-alkylperhydro derivatives 228 in a mixture  $\text{Et}_2\text{O}$  and THF at  $-40^\circ\text{C}$  in the presence of  $\text{CuI}$  in good yields (99TL3699).

3-Amino-6,6*a*,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine was reacted with ethyl 4,4,4-trifluoroacetoacetate in boiling benzene for 12-16 h, then the reaction mixture was concentrated *in vacuo* and the residue was treated with conc.  $\text{H}_2\text{SO}_4$  at  $100^\circ\text{C}$  to give tetracyclic 11-trifluoromethyl-1,2,3,4,4*a*,5,8,9-octahydropyrido[1',2';4,5][1,4]oxazino[3,2-*a*]quinolin-9-one in 30% yield (01MIP1).



3-Alkoxy-3-(4-biphenyl)perhydropyrido[1,2-*c*][1,4]oxazines were obtained from 3-hydroxy derivative with  $\text{PrOH}$  and  $\text{Br}(\text{CH}_2)_3\text{OH}$  in a boiling acidified medium (00JMC609, 00MIP13). Spontaneous dehydration of 11*b*-hydroxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinolin-4-one **258** in  $\text{CHCl}_3$  gave 3,4,6,7-tetrahydro derivative **259** (97JOC2080).

### 5. Reaction of Substituents Attached to Ring Carbon Atoms

Reaction of 3-(3-bromopropyl)-3-(4-biphenyl)perhydropyrido[1,2-*c*][1,4]oxazine with  $\text{AgNO}_3$  in a boiling solvent yielded 3-[(4-biphenyl)perhydropyrido[1,2-*c*][1,4]oxazin-3-yl]propyl nitrate (00MI9).

Treatment of an epimeric mixture of (4*S*,9*aS*)-4-phenylperhydropyrido[2,1-*c*][1,4]oxazin-1-oles with  $\text{HOCH}_2\text{CH}_2\text{OH}$  in  $\text{CHCl}_3$  at  $-10^\circ\text{C}$  in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  and then at room temperature for 3 days afforded an epimeric mixture of dioxolane derivatives (01EJOC2385). An epimeric mixture of (4'*S*,6'*R*,9*aS*)-4'-phenyl-6'-propylhexahydrospiro[1,3-dithiolane-2,8'(1'*H*)-pyrido[2,1-*c*][1,4]oxazin]-1'-ole was obtained by treatment of an epimeric mixture of (4*S*,6*R*,9*aS*)-1-hydroxy-4-phenyl-6-propylperhydropyrido[2,1-*c*][1,4]oxazin-8-one with ethanedithiol in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CHCl}_3$  at  $-10^\circ\text{C}$  (00JOC4435).

Epimeric mixtures of perhydropyrido[2,1-*c*][1,4]oxazin-1-oles (97SL799, 98T10309) and a 3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*c*][1,4]oxazin-1-ole (00SC2565) were prepared by desilylation of 1-trimethylsiloxy derivatives on the treatment with  $\text{Bu}_4\text{F}$  in THF and over  $\text{SiO}_2$  at  $100^\circ\text{C}$ , respectively. 9-Hydroxy-3-methoxy-1-phenyl-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazin-8-one (97EUP768302) and 10-hydroxy-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-carboxylate (96JAP(K)96/291144) were obtained by catalytic hydrogenation of the 9-benzyloxy and 10-benzyloxy derivative, respectively, over 5% Pd/C catalyst in MeOH.

Carboxyl group of (–)-9-fluoro-3-methyl-7-oxo-10-[(3*S*)-3-(*tert*-butoxycarbonylamino)pyrrolidino]-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was converted into 1-nitro-2-oxoethyl group in 45% yield by treatment with 1,1'-carbonyldiimidazole in boiling  $\text{CHCl}_3$  for 18 h, then with  $\text{MeNO}_2$  in the presence of  $\text{KOt-Bu}$  for another 18 h (96MI12). 6-(2,2-Diethoxycarbonyl)acetyl derivative formed from the aforementioned 6-carboxylic acid, when it was treated with 1,1'-carbonyldiimidazole in

boiling  $\text{CHCl}_3$ , then with  $\text{CH}_2(\text{COOEt})_2$  in boiling MeCN in the presence  $\text{K}_2\text{CO}_3$  in 14% yield.

4-Phenyl-9-(2-propoxycarbonylamino)perhydropyrido[2,1-*c*][1,4]oxazin-1-one was prepared from methyl 4-phenyl-1-oxoperhydropyrido[2,1-*c*][1,4]oxazine-9-carboxylate (98MIP12). First, the methyl ester was hydrolyzed into 9-carboxylic acid by heating in 6N HCl, then the carboxylic acid was reacted with  $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$  in benzene in the presence of  $\text{NEt}_3$  at 22 °C for 45 min, then at reflux for 50 min. After addition of *i*-PrOH the reaction mixture was boiled for 20 h to yield a 9-(*iso*-propoxycarbonylamino) derivative.

A side chain *tert*-butoxycarbamoyl group in pyrido[1,2,3-*de*]-1,4-benzoxazines converted into an amino group by treatment with diluted HCl in a solvent (96MI12, 98GEP19652219), or with TFA (96MI12). Cyclic nitrogen in the side-chain at position 10 of (3*S*)-(-)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids was acylated with carboxylic acid chlorides (98MIP19, 99MI23, 99MI58) and sulfonyl chlorides (99MI56). A side chain *N*-tosyl group was removed from a 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate, and the cyclic amino group was methylated (00MIP10). Piperazino NH group 9-fluoro-10-piperazino-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was reacted with 4-nitrobenzenesulfonyl chloride, 2,6-dichloropyrazine, 2,6-dichloropyridine in DMF in the presence of pyridine and with 4-nitrophenyl isothiocyanate in aqueous acetone in the presence of KOH (01MIP13).



The amino group of 8-amino-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinoline was reacted with *S*-methyl-2-thiophenecarboximide hydroiodide in DMSO in the presence of pyridine at 50 °C for 4 h to give amidine **260** (X = O) in 94% yield (97MIP4).

A side chain hydroxyl group in 5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one was changed for chloro atom by treatment with  $\text{SOCl}_2$  at room temperature for 16 h (98MIP13).

The respective amide was prepared from 7-substituted 5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids via acid chlorides with different benzylamines (00MIP3). 6-Carboxamides were *N*-benzylated, and a side-chain phenolic hydroxy group was *O*-alkylated. 7-Aryl-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was obtained from the ethyl ester by alkalic hydrolysis.

Heating of a mixture of ethyl 9-substituted 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates and 4-chlorobenzylamine yielded *N*-(4-chlorobenzyl)amides (01MIP2).

7-Methoxy derivative was obtained from 2-(4,5-dihydro-1*H*-imidazol-2-yl)-7-hydroxy-8-methyl-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one with methyl tosylate in DMF in the presence of K<sub>2</sub>CO<sub>3</sub> at 50 °C for 1 h (99EUP894796).

2-(4,5-Dihydro-1*H*-imidazol-2-yl) derivatives were prepared from ethyl 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-2-carboxylates and ethyl 5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-2-carboxylates with 2 M Me<sub>3</sub>Al in toluene and H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> at reflux temperature for 3 h (99EUP894796).

Reactions of 9-amino-2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine and its 5-oxo derivative with benzyl chloroformate in dioxane in the presence of NaHCO<sub>3</sub>, then with (*R*)-(-)-glycidyl butyrate in THF at -78 °C in the presence of BuLi gave 9-[(5*R*)-5-hydroxymethyl-2-oxo-3-oxazolidinyl] derivatives (99GEP19802239). Hydroxyl group was mesylated, and mesyloxy group was changed for azido group with NaN<sub>3</sub>, then azido group was converted into an amino group by the treatment with (MeO)<sub>3</sub>P. Amino group was reacted with acyl chloride and methyl chloroformate.

3-Aminoazetidin-2-ones were acylated with ofloxacin (**5**) by standard DCC-HOBT methodology (96MI14).

7-Oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids were prepared from 6-esters under acidic (96JAP(K)96/291144, 98MIP19, 98MI37, 99H(51)1563, 99MI36, 00MI76) and under alkalic conditions (00MIP10).

The decarboxylated 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-pyrido[1,2,3-*de*]-1,4-benzoxazine-7-one was isolated from **5** injection (96MI16), and from boiling HCl solution of **5** (97MI18) and its structure was confirmed by UV, IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass spectrometry.

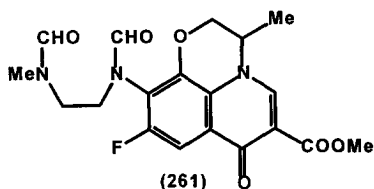
For further reaction see Section VII.B.4.

## 6. Ring Transformation

Reaction of 2-(4-nitrophenyl)pyrido[1,2,3-*de*]-1,4-benzoxazinium bromide in boiling AcOH with NH<sub>4</sub>OAc for 3.5 h, and with H<sub>2</sub>S in EtOH afforded 2-(4-nitrophenyl)pyrido[1,2,3-*de*]quinoxalinium bromide and 2-(4-nitrophenyl)pyrido[1,2,3-*de*]-1,4-benzothiazinium bromide, respectively (98MI45).

7. *Miscellaneous*

Ofloxacin (**5**) was resolved by electrokinetic chromatography using lipid A derivatives (97JAP(K)97/236581). Photostability (97PHA519, 98MI3, 98MI84, 01MI23) and photolytic reaction (99JOC5388, 99MI63) of **5** was studied. Ofloxacin was proved to be one of the most photostable fluoroquinoline-3-acid derivatives. Degradation of **5** in solution on the action of light, pH and ionic strength was investigated (97MI55). An 10-[*N''*-methyl-*N'*,*N''*-diformyl(2-aminoethyl)amino] derivative **261** was isolated from an aqueous photochemical reaction of **5** (99JOC5388). The photolysis of fluoroquinolones was investigated in neutral aqueous solution by ESR spectroscopy. Levofloxacin (**6**) did not generated free radicals in the process of photochemical degradation (98CPB1021). Among other fluoroquinoline-3-carboxylic acid antibacterial agents the electrochemical defluorination of **5** was also investigated (99H(51)1499).

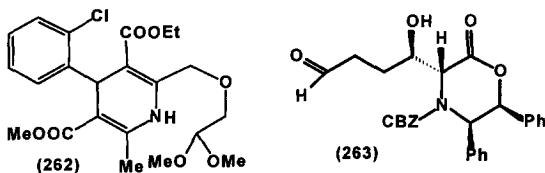


Preparation and usage of nitrate salt of **5** and pazufloxacin (**8**) were patented (01MIP14).

## C. SYNTHESIS

1. *By Formation of One Bond  $\alpha$  to the Bridgehead Nitrogen Atom [6+0( $\alpha$ )]*

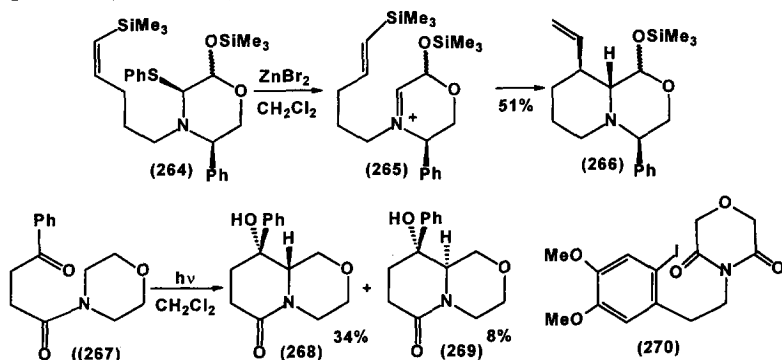
1*H*,8*H*-Pyrido[2,1-*c*][1,4]oxazine-7,9-carboxylate **245** was obtained by cyclization of 1,4-dihydropyridine-3,5-dicarboxylate **262** in boiling THF for 4 h in the presence of 3 N HCl (97CP2188071). Cyclization of methyl (-)-4-[(3*S*,5*R*)-6-oxo-5-phenylmorpholin-3-yl]butanoate in boiling toluene gave perhydropyrido[2,1-*c*][1,4]oxazine-3,6-dione **232** (00T233). Mild catalytic hydrogenation of oxazinone **263** over 5% Pd/C catalyst under 1 atm of hydrogen in CH<sub>2</sub>Cl<sub>2</sub> afforded 3,4-diphenyl-9-hydroxyperhydropyrido[2,1-*c*][1,4]oxazin-1-one (**226**) via sequential *N*-CBZ deprotection and reductive amination (98TL3659).



Reaction of 5-chloro-8-allyloxyquinoline with  $\text{Br}_2$  and  $\text{I}_2$  afforded 3-bromomethyl-, and 3-iodomethyl-8-chloro-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzoxazinium salts (96MI2). Heating of 8-(2-chloroethoxy)quinolines in benzene and toluene gave 2,3-dihydropyrido[1,2,3-*de*]-1,4-benzoxazinium chlorides (97MIP15).

## 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [ $6+0(\beta)$ ]

Treatment of an epimeric mixture of 4-substituted 2-(trimethylsilyloxy)-5-phenyl-3-phenylthio-1,4-oxazine **264** with  $\text{ZnBr}_2$  led to the stereoselective formation of perhydropyrido[2,1-*c*][1,4]oxazine **266** via the iminium ion **265** by the phenyl bearing stereocenter directed addition of the olefinic double bond from the  $\beta$ -face of the cyclic moiety (97SL799, 98T10309). Similarly, an epimeric mixture of (4*S*,9*aS*)-1-trimethylsilyloxy-4-phenyl-3,4,6,7-tetrahydropyrido[2,1-*c*][1,4]oxazine was prepared by cyclization of (*Z*)-5(*S*)-phenyl-3-phenylsulfanyl-2-trimethylsilyloxy-4-[4-(trimethylsilyl)but-3-enyl]morpholine (00SC2565).



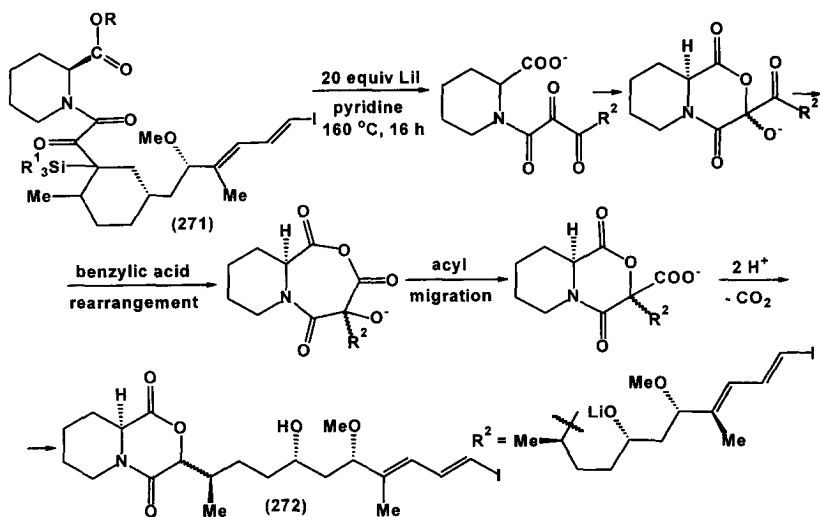
Irradiation of 4-(3-benzoylpropionyl)-1,4-morpholine (**267**) yielded an epimeric mixture of 9-hydroxy-9-phenylperhydropyrido[2,1-*c*][1,4]oxazin-6-ones **268** and **269** via hydrogen abstraction from the position 3 of the morpholine moiety of **267** (98T2529). It was assumed that the steric hinderance between the phenyl group and the hydrogen atoms of 5-methylene group of **267** in the biradicals contributed to the observed selectivity.

The Parham cyclization of the iodinated imide **270** by BuLi in dry THF at  $-78^{\circ}\text{C}$  afforded 11*b*-hydroxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazine[3,4-*a*]isoquinolin-4-one **258** (97JOC2080). Iodide–lithium exchange was faster than addition to the carbonyl group of imide **270** and intramolecular cyclization of the initially formed anion gave compound **258**.

3. By Formation of One Bond  $\gamma$  to the Bridgehead Nitrogen  
Atom [6+0( $\gamma$ )]

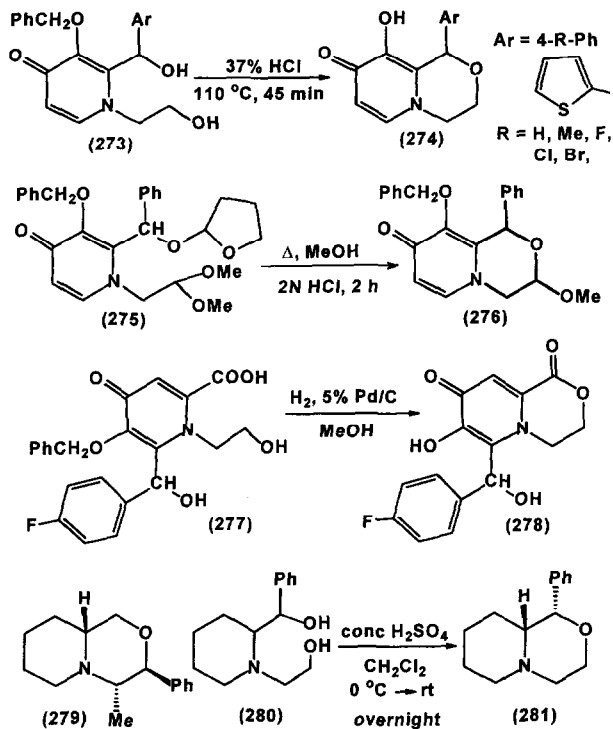
A 1:1 mixture of perhydropyrido[2,1-*c*][1,4]oxazine-1,4-diones **272** was obtained, instead of the expected pipecolic acid derivative **271** ( $\text{R}=\text{H}$ ,  $\text{R}^1=\text{Et}$ ), when the triethylsilyl ether **271** ( $\text{R}=\text{Me}$ ,  $\text{R}^1=\text{Et}$ ) at a higher concentration ( $c > 0.017\text{ M}$ ), or trimethylsilyl ether **271** ( $\text{R}=\text{R}^1=\text{Me}$ ) was treated with LiI (20 equiv.) in pyridine (Scheme 8) (97JA962).

Heating 1-(2-hydroxyethyl)-2-(1-aryl-1-hydroxymethyl)-3-benzyloxy-1,4-dihydropyridin-4-ones **273** in 37% HCl gave 1-aryl-9-hydroxy-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazin-8-ones **274** (97EUP768302). A diastereomeric mixture of 9-benzyloxy-3-methoxy-1-phenyl-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazin-8-one (**276**) was obtained when 1,4-dihydropyridine **275** was heated in the presence of 2 N HCl (97EUP768302). Catalytic hydrogenation of 4-oxo-1,4-dihydropyridine-2-carboxylic acid **277** over 5% Pd/C catalyst yielded 6-[(4-fluorophenyl)hydroxymethyl]-7-hydroxy-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazine-1,8-dione (**278**) (97EUP768302).

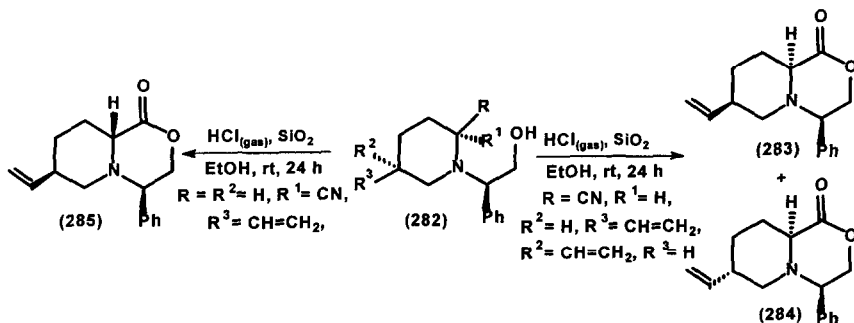


Scheme 8



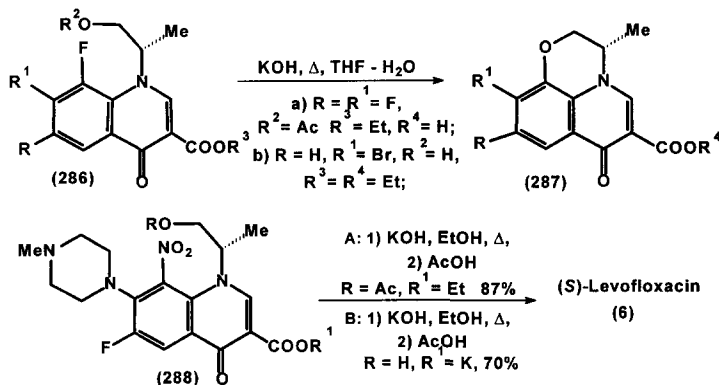


A single stereoisomer of 4-methyl-3-phenylperhydropyrido[2,1-*c*][1,4]oxazine **279**, containing a *trans*-fused bicycle, was obtained by the cyclization of 1-(2-hydroxyethyl)-2-piperidinemethanol **235** in CH<sub>2</sub>Cl<sub>2</sub> on the action of conc. H<sub>2</sub>SO<sub>4</sub> (97JHC1813). Similarly, 1-phenylperhydropyrido[2,1-*c*][1,4]oxazine **281** was obtained from 1-(2-hydroxyethyl)-2-[(phenyl)hydroxymethyl]piperidine **280**.



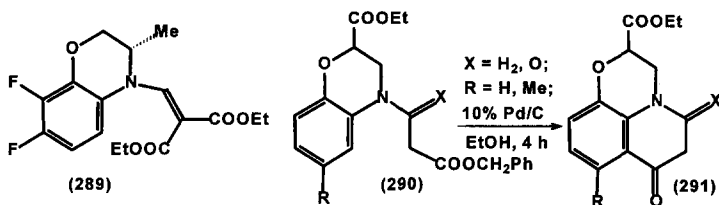
Treatment of 1-(2-hydroxyethyl)-2-cyanopiperidines **282** with HCl gas in the presence of SiO<sub>2</sub> afforded perhydropyrido[2,1-*c*][1,4]oxazin-1-ones **283–285** (00TA3913).

Ring closure of 1-(2-chloroethyl)-6-fluoro-4-oxo-1,4-dihydroquinoline-2-carboxylate on the action of K<sub>2</sub>CO<sub>3</sub> in DMF at 100 °C for afforded 8-fluoro-1,2-dihydro-4*H*,6*H*-[1,4]oxazino[4,3-*a*]quinoline-4,6-dione (01SL833).



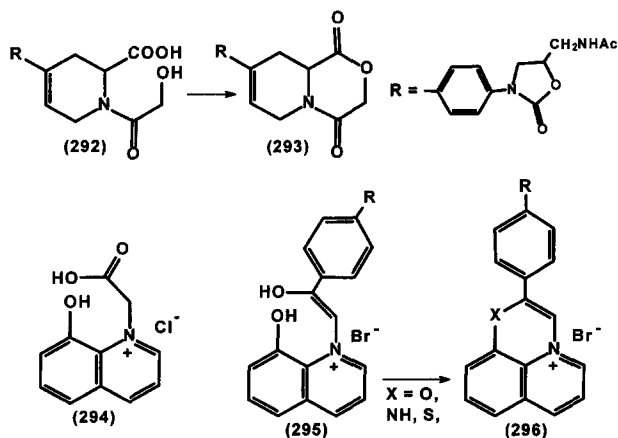
The intermediate **287** (R = R<sup>1</sup> = F, R<sup>4</sup> = H) of **6** was prepared by the cyclization of 1-substituted 6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates **286** (R = R<sup>1</sup> = F, R<sup>2</sup> = Ac, R<sup>3</sup> = Et) in the presence of KOH (97H(45)137). Ethyl (3*S*)-10-bromo-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**287**, R = H, R<sup>1</sup> = Br, R<sup>4</sup> = Et) was obtained by cyclization of quinoline-3-carboxylate **286** (R = H, R<sup>1</sup> = Br, R<sup>2</sup> = OH, R<sup>3</sup> = Et) (00MIP10). Levofloxacin (**6**) was prepared by cyclization of quinoline-3-carboxylates **288** (00MIP11). Diethyl (1,4-benzoxazin-4-yl)methylenemalonate **289** was cyclized on the action of PPE (98MI37, 98MIP19, 99MI36), and that of Ac<sub>2</sub>O in conc. H<sub>2</sub>SO<sub>4</sub> (98MI49), to give ethyl ester of **287** (R = R<sup>1</sup> = F, R<sup>4</sup> = Et). Ofloxacin (**5**) was obtained by cyclization of 6,8-difluoro-7-(4-methyl-1-piperazinyl)-1-[1-(acetoxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate in the presence of NaOH in *i*-PrOH at 100 °C (01JAP(K)01/31654). The racemic mixture of **289** and its 8-methylthio derivatives were also cyclized by treatment with a 1:2 mixture of Ac<sub>2</sub>O and conc. H<sub>2</sub>SO<sub>4</sub> at 50 °C (99H(51)1563). Cyclization of diethyl {[7-(4-morpholinylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl]methylene}malonate on the action of a mixture of P<sub>2</sub>O<sub>5</sub> and MeSO<sub>3</sub>H in CH<sub>2</sub>Cl<sub>2</sub> at 50 °C for 18 h gave 9-(4-morpholinylmethyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (01MIP2). Treatment of diethyl (3*S*)-[7-(8-difluoro-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)methylene]malonate with BF<sub>3</sub>·Et<sub>2</sub>O in Ac<sub>2</sub>O at 140 °C for 1 h

gave (3*S*)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid derivative **252** ( $X = F$ ,  $R = BF_2$ ,  $R^1 = Me$ ) (01MIP10).



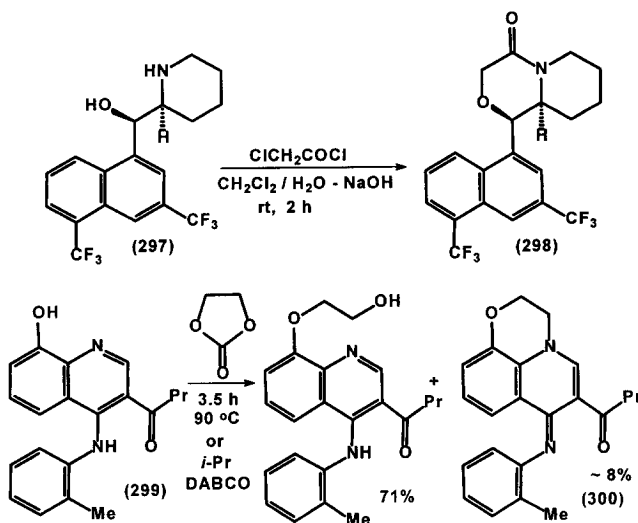
7-Oxo-2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-2-carboxylates (**291**,  $X = H_2$ ) were obtained by hydrogenation of 4-substituted 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates (**290**,  $X = H_2$ ) over 10% Pd/C catalyst, then by the treatment of free acids with  $(CF_3CO)_2O$  (99EUP894796). 5,7-Dioxo-2,3,6,7-tetrahydro derivatives **291** ( $X = O$ ) were prepared similarly from **290** ( $X = O$ ). The products **291** ( $X = O$ ) exist in 7-hydroxy-5-oxo-2,3-dihydro-5*H* tautomeric form.

1,3,4,6,9*a*-Hexahydropyrido[2,1-*c*][1,4]oxazine-1,4-diones **293** were prepared by the cyclization of 4-substituted 1-(2-hydroxyacetyl)-1,2,3,6-tetrahydropyridine-2-carboxylic acids **292** with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide in the presence of dimethoxypyridine (99MIP3).



Heating of 8-hydroxyquinolinium chloride **294** on a sand bath without solvent in the presence of catalytic amount of piperidine for 30 min yielded 2-oxo-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzoxazinium chloride (**253**) (98MI45). Similar reactions of compound **295** afforded 2-arylpyrido[1,2,3-*de*]-1,4-benzoxazinium bromides (**296**,  $X = O$ ).

Cyclization of 1-(2-fluoro-4-nitrophenyl)-2-hydroxymethylpiperidine in boiling THF in the presence of 60% NaH for 16h afforded 3-nitro-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine (00MIP1).



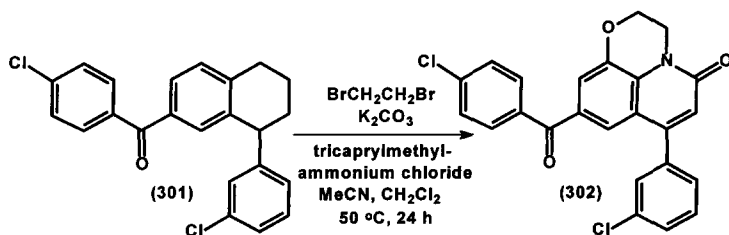
#### 4. By Formation of Two Bonds from [4+2] Atom Fragments

( $\pm$ )-(3*R*,4*R*,9*aS*)-4-Methyl-3-phenylperhydropyrido[2,1-*c*][1,4]oxazin-3-ol (**234**) was prepared in the reaction of 2-piperidinemethanol and 2-bromopropiophenone in boiling MeCN for 16h (97JHC1813). 3-Hydroxy-3-(4-biphenyl)perhydropyrido[1,2-*c*][1,4]oxazine was obtained in the reaction of 2-piperidinemethanol and 4-bromoacetyl biphenyl in a mixture of acetone and  $\text{Et}_2\text{O}$  at room temperature (00JMC609, 00MIP13). Perhydropyrido[1,2-*c*][1,4]oxazin-1-one **298** was obtained in the reaction of quinoline derivative **297** and chloroacetyl chloride (00MIP1).

6-Butyl-2,3-dihydro-7-[(2-methylphenyl)imino]-7H-pyrido[1,2,3-*de*]-1,4-benzoxazine (**300**) was isolated as a by-product from the reaction mixture of 3-butyl-8-hydroxy-4-(2-methylphenylamino)quinoline (**299**) in molten ethylene carbonate at  $90^\circ\text{C}$ , or in boiling *i*-PrOH in the presence of DABCO (97MI30). The formation of side-products could be avoided when the reaction was carried out in boiling *t*-BuOH.

Cyclocondensation of 8-hydroxyquinolin-2(1*H*)-one and chloroacetone in the presence of  $\text{K}_2\text{CO}_3$  in dry DMF at ambient temperature for 24h afforded 2,3-dihydro-3-hydroxy-3-methyl-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one (**240**,  $\text{R} = \text{Me}$ ) (97HCA1161). A tautomeric mixture of ring-opened

**241** ( $R = Ar$ ) and cyclized tricyclic compound **240** ( $R = Ar$ ) was obtained when 2-bromoacetophenones were reacted with 8-hydroxyquinolin-2(1*H*)-one under the above conditions. Presence of a 4-methoxy substituent shifted the equilibrium to the ring-opened product **241** ( $R = 4\text{-MeOPh}$ ), while that of 4-nitro group gave only cyclized product **240** ( $R = \text{NO}_2$ ). Similarly, mixtures of ring-opened and 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one derivatives were formed in the reaction of 8-hydroxy-1,2,3,4-tetrahydroquinolin-2-one and halomethyl ketones (00HCA349).



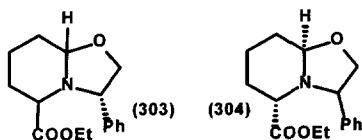
Cyclocondensation of 8-hydroxyquinolin-2(1*H*)-one **301** with  $\text{BrCH}_2\text{CH}_2\text{Br}$  afforded 2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one **302** (98MIP13).

### 5. By Formation of Two Bonds from [3+3] Atom Fragments

Ethyl 7-hydroxy-3-methyl-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate was obtained by cyclocondensation of 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine and triethyl methanetricarboxylate (00M13).

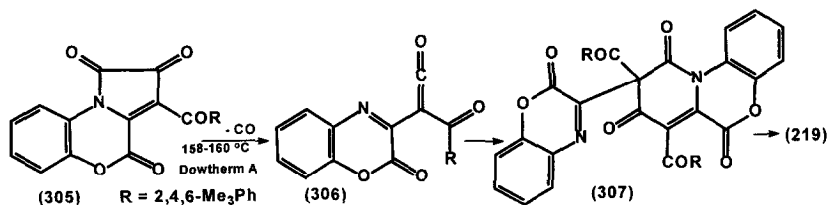
### 6. Ring Transformations

Treatment of 3-phenylperhydro[1,3]oxazolo[3,2-*a*]pyridine-5-carboxylates **303** and **304** with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in THF, followed by reduction with  $\text{NaBD}_4$  afforded 6-deutero-4-phenylperhydropyrido[2,1-*c*][1,4]oxazin-1-ones **220** and **222** (97JA6446).



Thermal decomposition of 3-(2,4,6-trimethylbenzoyl)-1,2-dihydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-trione (**305**) in Dowtherm A yielded 6,8,9,10-tetrahydropyrido[2,1-*c*][1,4]benzoxazine **219** by [4+2] cycloaddition

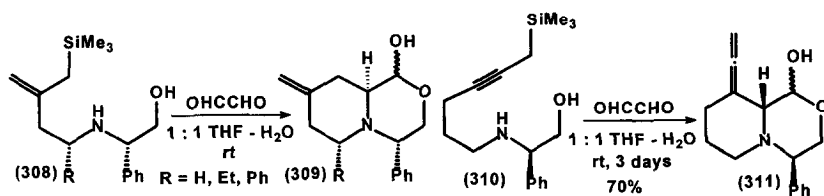
of the primarily formed ketene **306** and the subsequent rearrangement of 6,8,9,10-tetrahydropyrido[2,1-*c*][1,4]benzoxazine-6,8,10-trione **307** (99MI40).



Catalytic hydrogenation of (4'*S*,6'*R*,9'*aS*)-4'-phenyl-6'-propylhexahydrospiro[1,3-dithiolane-2,8'(1'*H*)-pyrido[2,1-*c*][1,4]oxazin]-1'-one over Raney Ni in MeOH gave (4*S*,6*R*,9*aS*)-4-phenyl-6-propylperhydro[2,1-*c*][1,4]oxazin-1-one (00JOC4435).

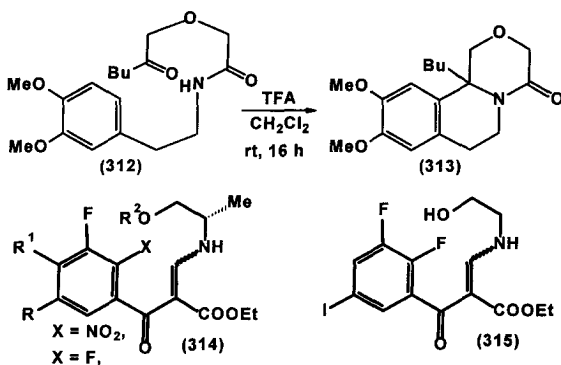
## 7. Miscellaneous

Levofloxacin (**6**) was enantioselectively obtained by the enzymatic hydrolysis of ofloxacin butyl ester by immobilization of porcine liver esterase (01MI25, 01MI32).

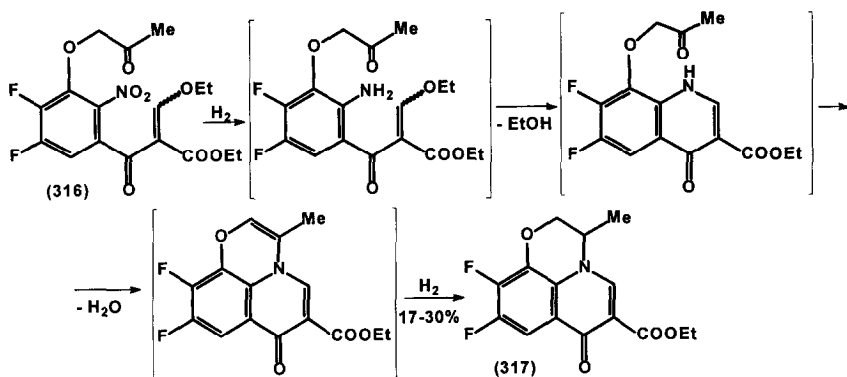


Reaction of 40% glyoxal with silylated compounds **308** (97SL799, 99SL1094, 00JOC4435) and **310** (97SL799) gave a diastereomeric mixture of 1-hydroxy-4-phenylperhydropyrido[2,1-*c*][1,4]oxazines **309** and **311**, respectively. Similarly, diastereomeric mixtures of 8-substituted 1-hydroxy-4-phenylperhydropyrido[2,1-*c*][1,4]oxazines were prepared (01EJOC2385).

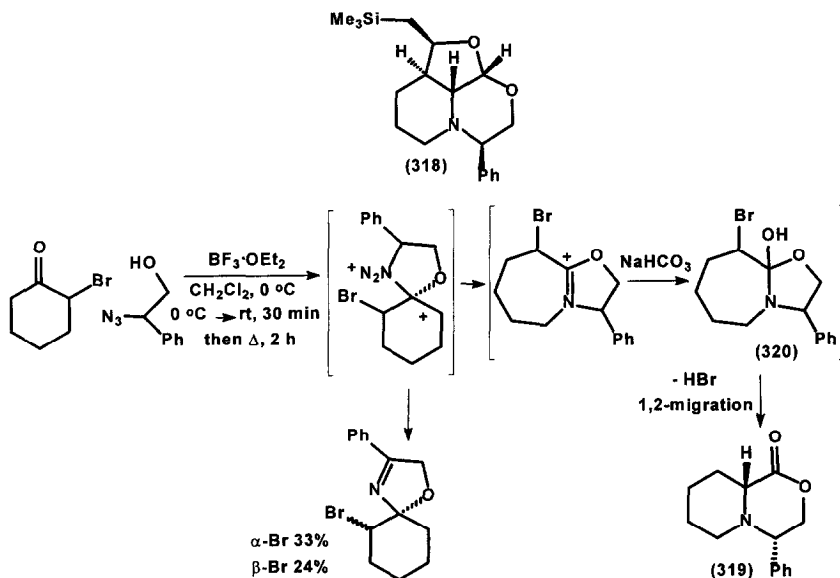
Cyclization of amide **312** by treatment with TFA gave 11*b*-butyl-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinolin-4-one **313** (97JOC2080).



Intermediate **287** ( $R = R^1 = F$ ,  $R^4 = H$ ) of **6** was obtained in excellent yield when (*S*)-*a*-minoacrylates **314** ( $R = R^1 = F$ ,  $R^2 = \text{Ac}$ ,  $X = F$ ,  $\text{NO}_2$ ) were treated with 110 mol% of powdered KOH in THF at 0°C to ambient temperature for 1 h and the formed quinoline-3-carboxylate **286** ( $R^2 = \text{Ac}$ ) was treated without isolation with a 10% aqueous KOH at reflux temperature for 2 h (97H(45)137). The addition of KOH in two portions was essential for good yield. 9,10-Difluoro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was similarly prepared starting from the racemic dialkyl,*tert*-butylsilyloxy derivative of **314** ( $R = R^1 = F$ ,  $R^2 = \text{alkyl}_2, t\text{-BuSi}$ ,  $X = F$ ,  $\text{NO}_2$ ) in the presence of different base (99USP5952494). Treatment of compound **314** ( $R = R^1 = X = F$ ,  $R^2 = H$ ), prepared from L-alaninol,  $\text{K}_2\text{CO}_3$  and  $\text{Bu}_4\text{NBr}$  in boiling *o*-xylene yielded 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate **287** ( $R = R^1 = F$ ,  $R^4 = \text{Et}$ ) (01JAP(K)01/172283). (3*S*)-3-Methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate **287** ( $R = R^1 = F$ ,  $R^4 = \text{Et}$ ) was obtained when ethyl (2,3,4,5-tetrafluorobenzoyl)-2-[(2*S*)-3-hydroxy-2-propyl]aminomethylene}acetate was treated with  $\text{K}_2\text{CO}_3$  in DMF at 120°C for 8 h (00MI76). Ethyl (3*S*)-10-bromo-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**287**,  $R = H$ ,  $R^1 = \text{Br}$ ,  $R^4 = \text{Et}$ ) was prepared by cyclization of aroylacetate **314** ( $R = H$ ,  $R^1 = \text{Br}$ ,  $R^2 = H$ ,  $X = F$ ) (00MIP10). 9,10-Difluoro-3(*S*)-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid and its racemic form were prepared in the reaction of ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-2-ethoxymethyleneacetate and (*R*)- or (*R,S*)-2-aminopropanol and subsequent hydrolysis of the ring closed tricyclic esters (98MI45). Cyclization of ethyl 2-(2,3-difluoro-5-iodobenzoyl)-2-[*N*-(2-hydroxyethyl)aminomethylene]acetate **315** in the presence of  $\text{K}_2\text{CO}_3$  in DMF at 95°C for 3.5 h yielded 9-iodo-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (01MIP2).



9,10-Difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylate **317** was obtained by the catalytic hydrogenation of aroylacetate **316** over different catalyst {20%  $Pd(OH)_2/C$ , 10%  $Pd/C$ , Raney Ni,  $PtO_2$ ] (99MI55). Treatment of tricyclic nitrogen bridgehead compound **318** with  $Bu_4NF$  in boiling THF gave  $\alpha$ -4,9,9a-H- $\beta$ -1-H-4-phenyl-9-vinylperhydropyrido[2,1-c][1,4]oxazin-1-ol (98T10309).



A single isomer of 4-phenylperhydropyrido[2,1-c][1,4]oxazin-1-one **319** was isolated from a reaction mixture of 2-bromocyclohexane and 2-azido-2-phenylethanol. The formation of **319** was deduced from azepino[1,2-b]



[1,3]oxazole intermediate **320** by HBr elimination and 1,2-migration (00JOC3771).

Graphical synthetic routes of pazufloxacin (**8**) was reported (99MI25).

#### D. APPLICATIONS AND IMPORTANT COMPOUNDS

Optically active and deuterated pipercolinic acid derivatives were prepared via 4-phenylperhydropyrido[2,1-*c*][1,4]oxazin-1-ones (97JA6446, 97SL799, 98EJOC2461, 98T10309, 98TL3659, 00JOC4435, 00SC2565, 00TA3913, 01EJOC2385).

(7*S*,8*R*,9*R*,9*aR*)-7,8,9-trihydroxyperhydropyrido[2,1-*c*][1,4]oxazine was patented for treating hepatitis virus infection (00MIP14). 7-Substituted 5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxamides were patented as tachykinin antagonists (00MIP3). 9-Fluoro-3-methyl-10-[(4-isopropyl)-2-thiazolyl)methoxy]-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was patented as drug discharge pump inhibitors (01MIP7).

Antimicrobial activity and mechanism of action (96MI1), pharmacokinetics (96MI3) of ofloxacin (**5**) and resistance mutations in mycobacterium tuberculosis against fluoroquinolones, including **5** (96MI9), furthermore the usage of **5** in clinics (97MI22), in the therapy of mycobacterioses (97MI6), and in the management of genitourinary tract infections (98MI93) were reviewed. The effects of subinhibitory concentrations of **5** on the surface hydrophobicity of a clinical isolate of *Salmonella enteritidis* were studied (98AF697). Ofloxacin did not influence the uptake of pefloxacin (97MI36). Binding sites of DNA gyrase-DNA complex for **5** were investigated (99MI62). The role of **5** and levofloxacin (**6**) in the treatment of tuberculosis was reviewed (01MI21).

Ofloxacin (**5**) was applied in a slow-release formulation in a combination with a reversible proton-pump inhibitor (97MIP2), and with pantoprazole (97MIP1). Application of **5** in ophthalmic (97MIP3), in otic composition (97MIP7), preparation of aqueous formulation of **5** (99MIP12, 00MIP9, 01JAP(K)01/48807), and that of water-soluble powder (00MIP21) were patented. Ofloxacin (**5**) was claimed to use in a combination with antimicrobial peptides (97MIP9), with other agents as remedies or preventives for AIDS (97MIP8). Pharmaceutical formulations of **5** were reviewed (98MI7).

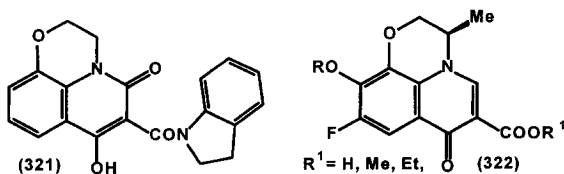
Antimicrobial activities (98MI12, 00MI64), pharmacology, pharmacokinetics (00MI19, 00MI23, 00MI58), clinical pharmacokinetics (97MI20), clinical efficacy, pharmacodynamics (00MI19, 00MI23), adverse effects, cardiovascular side effects (00MI15), toxicity profiles (99MI15), drug interaction of levofloxacin (**6**), and its usage in infection of the respiratory

tract, skin, soft tissues and urinary tract (98MI94, 98MI72, 99MI60, 00MI7), in CNS infections (01MI33), in the treatment of community-acquired pneumonia (01MI31), in therapy (98MI98), and in the treatment of anaerobic infections (96MI4) were reviewed. A risk-benefit assessment of **6** in the treatment of respiratory, skin, skin structure, and urinary tract infections was published (01MI24). Antibacterial activity of **6** was compared with that of sparfloxacin (97MI54, 98MI55) and that of trovafloxacin (97MI63).

Comperative pharmacokinetics and pharmacodynamics of fluoroquinolones, including **5** and **6** were reviewed (01MI27). Glucoronidation metabolism of enantiomers of **5** in rat microsomes treated with different inducers was studied (00MI62). Pharmacokinetics of fluoroquinolones, including **5** and **6**, in patients with renal impairment were reviewed (00MI39). Antimicrobial pharmacology and ocular pharmacokinetics of ophthalmic solutions of **6** were reviewed (00MI56).

Low photosensitizing potential of **6** was justified in healthy volunteers (00MI26). Photophysical and photobiological properties of **5** (99MI64, 00MI38, 00MI65, 01MI5, 01MI16) and **6** (00MI37, 01MI5) were investigated.

Pazufloxacin (**8**), an antibacterial agent, is under development. Its *in vitro* and *in vivo* activities were intensively investigated (99MI1, 99MI3, 99MI4, 99MI7, 99MI9, 99MI12, 99MI29). Its synthesis, pharmacology, metabolism, and clinical development were reviewed (00MI70). Histamine-releasing properties of **8** in intravenous usage were studied (98MI36, 98MI68, 98MI69, 98MI96). Intravenous toxicities of **8** were investigated (98MI76, 98MI78, 98MI81, 98MI85). Pharmacokinetics of **8** were evaluated in elderly patients (97MI19, 98MI50, 99MI22), in elderly volunteers (00MI28), and in patients with reduced renal function (00MI29). Therapeutic effects of **8** against polymicrobial infections in the uterine endometritis model (98MI21) and its general pharmacology (99MI27, 99MI28) were reported. A sustained-release formulation of **8** for treatment of myelitis was patented (97JAP(K)97/124486). Phase I clinical study of pazufloxacin mesilate was also reported (99MI30). Clinical efficacy of **8** against Gonorrhea was determined (98AAC579). Usage of **5**, **6**, and **8** for the topical and/or local treatment of diseases, caused by bacteria was patented (01MIP16). Nitrate salt of **5** and **8** was patented (01MIP14).



Toxicological potentials and disposition of **218** (DV-7751a) administered orally to immature beagle dogs and nature cynomolgus monkeys were investigated (97MI40). 5*H*-Pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one **321** was claimed as inhibitor for IgE antibody formation (98JAP(K)98/324631). 10-Alkoxy-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid derivatives **322** were patented as platelet aggregation inhibitors (96JAP(K)96/291144). 10-Substituted 9-fluoro-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-carboxylic acids were investigated and patented as antimycoplasma agents (98MIP19, 99MI23, 99MI24). Anti-HIV activity of 9-fluoro-3-methyl-10-[4-(2-pyrimidyl)piperazin-1-yl]-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-carboxylic acids was investigated (99BMCL3063).

After 2-year treatment of *Euglena gracilis* cells with *N*-succinimidyl-ofloxacin a number of anomalous mitochondria have been observed (98MI83). Preparation and application of carbon-coated PVC membrane ofloxacin-selective electrode was reported (98MI25). Blended membranes of ofloxacin–chitosan–gelatin was characterized by IR and X-ray diffraction (00MI24). An ofloxacin sensing membrane based on fluorescence quenching of a fluorescent reagent was prepared and characterized (00MI35).

## VIII. Pyrido[2,1-*c*][1,4]thiazines and Their Benzologs

### A. STRUCTURE

#### 1. Thermodynamic Aspects

Plasma protein binding of **7** was investigated by ultrafiltration method (98JPS215, 98MI91). Apparent partition coefficient of **7** was determined at 25°C at pH 7.4 in H<sub>2</sub>O/*n*-octanol system to be  $-0.29$  (98JPS215). Rufloxacin (**7**) was determined in biological fluids (98JC(A)343, 99MI8, 00MI45) and formulated products (98MI71) by HPLC, in human urine by Eu(III) ion sensitized fluorometry (01MI10), and in capsules and urine by single sweep oscillopolarography (01MI11). Thermal stability and decomposition of **7** were investigated by using TG and DSC (00MI46).

#### 2. Theoretical Calculations

Blood–brain barrier permeation of **7**, among other drugs, was predicted from its three-dimensional molecular structure by a computational method (00JMC2204). The combination of molecular topological methods using 137 quinolones, including **7** provided an excellent tool for the design of new

antibacterial quinolones (AAC2764). The anti-toxoplasma activities of 24 quinolones, including **7**, were examined by means of linear discriminant analysis using topological indexes as structural descriptors (00AAC2771).

### 3. *Mass Spectroscopy*

Electron impact/Fourier transform ion cyclotron resonance mass spectrometry was used to study the mass spectrum of **7** (96MI20).

## B. REACTIVITY

### 1. *Reduction*

Ethyl (3*S*)-8-amino-3-methyl-10-(2,6-dimethyl-4-pyridyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate was obtained by the reduction of the respective 8-nitro derivative (00MIP10).

### 2. *Oxidation*

Oxidation of 7-hydroxy- and 7-aryl-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates and 6-carboxamides with 3-chloroperoxybenzoic acid in CH<sub>2</sub>Cl<sub>2</sub> yielded sulfoxides and sulfones, depending on the molar ratio of the substrate and oxidizing agent (00MIP7). A sulfoxide was prepared by the oxidation of ethyl (3*S*)-3-methyl-10-(2,6-dimethyl-4-pyridyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate (00MIP10).

### 3. *Reactivity of Ring Carbon Atoms*

Nitration of ethyl (3*S*)-3-methyl-10-(2,6-dimethyl-4-pyridyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate gave 8-nitro derivative (00MIP10).

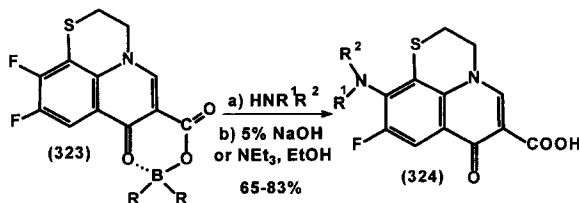
2-(4-Nitrophenyl)pyrido[1,2,3-*de*]-1,4-benzothiazinium bromide (**296**, X = S, R = NO<sub>2</sub>) reacted with heterocyclic quaternary salt **254** in position 7 to give a monomethine cyanine dye **257** (X = S, R = NO<sub>2</sub>) (98MI45).

Bromo atom of ethyl (3*S*)-10-bromo-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate was changed for heteroaryl groups with tributylstannyl derivatives of heterocycles in the presence of (Ph<sub>3</sub>P)<sub>2</sub>Pd(II)Cl<sub>2</sub> in boiling toluene (00MIP10). 7-Aryl-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates, 6-carboxamides and their 1,1-dioxide derivatives were prepared from 7-chloro derivatives in the

presence of  $(\text{Ph}_3\text{P})_4\text{Pd}$  and  $\text{Na}_2\text{CO}_3$  (00MIP7). Ethyl 7-chloro-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate-1,1-dioxide was prepared from the 7-hydroxy derivative by treatment with  $\text{Ph}_3\text{P}$  and  $\text{CCl}_4$  in MeCN.

#### 4. Reactivity of Substituent Attached to Ring Carbon Atoms

Reaction of 9,10-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid and its ethyl ester with  $\text{B}(\text{OH})_3$  in  $\text{Ac}_2\text{O}$  in the presence of  $\text{ZnCl}_2$  afforded 6-[(diacetoxyboryl)oxycarbonyl] derivative **323** ( $\text{R} = \text{OAc}$ ), which was reacted with primary and cyclic amines to give 10-amino-9-fluoro-7-carboxylic acid derivatives **324** (97MI41, 98MI30). 6-[(Difluoroboryl)oxycarbonyl] derivative **323** ( $\text{R} = \text{F}$ ) was obtained from ethyl 9,10-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate with  $\text{BF}_3 \cdot \text{THF}$  complex. Reaction of **323** ( $\text{R} = \text{F}$ ) and 1-methylpiperazine in DMF at 50–60 °C and subsequent acidic hydrolysis afforded **7** (97MI1).



Hydrolysis of ethyl 9-fluoro-10-(4-methylpiperazino)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate in a boiling mixture of AcOH and 35% HCl afforded **7** · HCl (97USP5703233). That of (3*S*)-3-methyl-10-(2,6-dimethyl-4-pyridyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate gave the 6-carboxylic acid (00MIP10). 7-Oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid was obtained from its ethyl ester by alkalic hydrolysis in 20% yield (99AP19).

Piperazine NH group of 9-fluoro-10-(1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate was reacted with 4-nitrophenylsulfonyl chloride, 2,6-dichloropyrazine, 2,6-dichloropyridine in DMF in the presence of pyridine, and with 4-nitrophenyl isothiocyanate in aqueous acetone in the presence of KOH (01MIP13). A side chain amino group on a 2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazin-7-one skeleton was acylated (00MIP10).

7-Aryl-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxamides and their 1,1-dioxides were prepared from the respective

6-carboxylates through 6-carboxylic acids and 6-acid chlorides with benzylamines (00MIP7).

Rufloxacin degraded with UVA radiation under anaerobic and aerobic conditions by decarboxylation (98MI5).

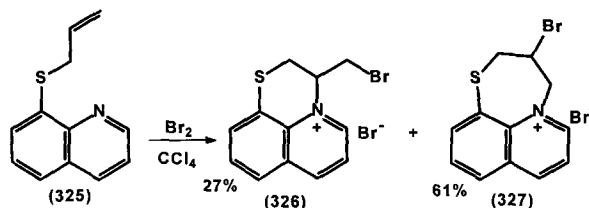
### 5. Miscellaneous

Photochemistry, photophysical properties and photosensitization of **7** were investigated (99MI37, 99MI42, 99MI64, 01MI23). Preparation and usage of nitrate salt of **7** were patented (01MIP14).

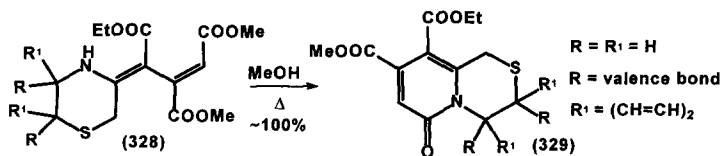
## C. SYNTHESIS

### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6+0( $\alpha$ )]

Ethyl 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate was prepared by cyclization of diethyl (2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methylenemalonate in PPA at 160 °C for 1 h (99AP19).



3-Iodomethyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium triiodide was obtained from 8-allylthioquinoline (**325**) by treatment with  $\text{I}_2$  in a solvent (acetone,  $\text{Et}_2\text{O}$ ,  $\text{EtOH}$  and  $\text{CHCl}_3$ ) and with  $\text{HI}$  and 30%  $\text{H}_2\text{O}_2$  in *i*- $\text{PrOH}$  (97CHE989). Treatment of triiodide with  $\text{NaI}$  gave iodide salt, which could be converted back to triiodide with  $\text{I}_2$ . Reaction of **325** with 3-iodomethyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium triiodide in acetone at room temperature yielded 3-iodomethyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium iodide. Reaction of **325** and  $\text{Br}_2$  afforded a mixture of 3-bromomethyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium bromide (**326**) and 3-bromomethyl-3,4-dihydro-2*H*-pyrido[1,2,3-*ef*]-1,5-benzothiazepinium bromide (**327**) (97CHE989).

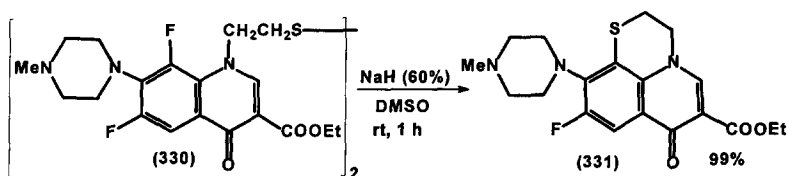


Pyrido[2,1-*c*][1,4]thiazine-8,9-dicarboxylate and pyrido[2,1-*c*][1,4]benzothiazine-7,8-dicarboxylate **329** were obtained by cyclization of tricarboxylates **328** (99T7915).

Some further synthesis methods are mentioned in Section VIII, C.5.

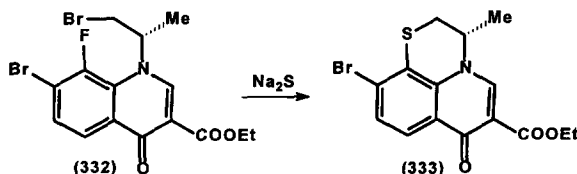
## 2. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6+0( $\gamma$ )]

Treatment of quinolone disulfide **330** with NaH yielded rufloxacin ethyl ester (**331**) (97USP5703233).



## 3. By Formation of Two Bonds from [5+1] Atom Fragments

(3*S*)-10-Bromo-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate **333** was prepared in the reaction of 1-(2-bromo-1-methylethyl)-7-bromo-8-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **332** and Na<sub>2</sub>S (00MIP10).

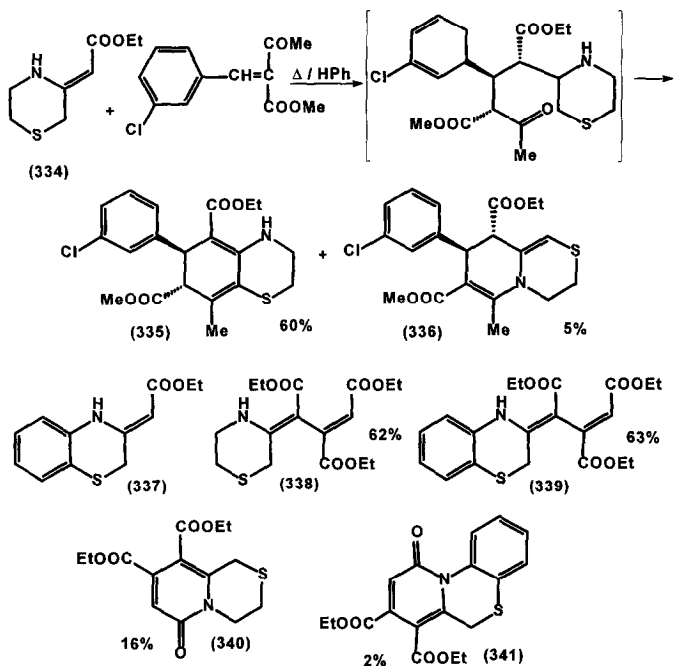


## 4. By Formation of Two Bonds from [4+2] Atom Fragments

1-Phenyl-1,2-dihydropyrido[1,2,3-*de*]-1,4-benzoxazonium perchlorate was prepared in the reaction of 8-quinolinesulfonyl chloride and styrene in MeCN in the presence of LiClO<sub>4</sub> at room temperature (01CHE382).

## 5. By Formation of Two Bonds from [3+3] Atom Fragments

A 3,4,8,9-tetrahydropyrido[2,1-*c*][1,4]thiazine **336** and a benzo(*b*)-1,4-thiazine **335** was isolated from the reaction mixture of enaminone **334** and 2-(3-chlorobenzylidene)acetylacetate (99T7915). Reactions of enamines **334** and **337** with DMAD in MeOH yielded addition products **338** and **339** and bi- and tricyclic derivatives **340** and **341**, respectively. The latter could be obtained in quantitative yields when the addition products **338** and **339** were heated in refluxing MeOH.



Cyclocondensation of 3,4-dihydro-2*H*-1,4-benzothiazines and diethyl ethoxymethylenemalonate in PPA at 120–160°C yielded ethyl 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]benzothiazine-6-carboxylates (97MI3, 99AP19), or 6-carboxylic acids by subsequent hydrolysis (97MI41, 98MI30).

## 6. Ring Transformation

Reaction of 2-(4-nitrophenyl)pyrido[1,2,3-*de*]-1,4-benzoxazinium bromide (**296**, X = O, R = NO<sub>2</sub>) with H<sub>2</sub>S in EtOH afforded 2-(4-nitrophenyl)pyrido[1,2,3-*de*]-1,4-benzothiazinium bromide (**296**, X = S, R = NO<sub>2</sub>) (98MI45).



## D. APPLICATIONS AND IMPORTANT COMPOUNDS

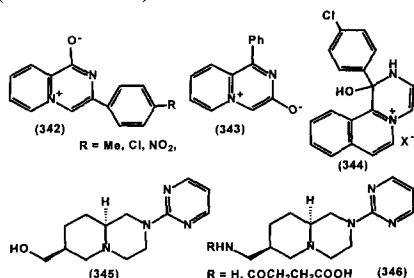
Photosensitization (96MI7, 98MI5), pharmacokinetics (97MI8), penetration into the cerebrospinal fluid in patients (00AAC73), and interaction with theophylline (98AAC2359) of rufloxacin (**7**) and activities of an active metabolite (97AAC927) of **7** were evaluated. *In vitro* and *in vivo* antibacterial activities of **7** were compared with those of other antibacterial agents (96MI21, 97MI3, 97MI11, 97MI43, 97MI47, 98MI16, 98MI18, 98MI52, 98MI82). Immunoregulation by **7** was reviewed (00MI72). Rufloxacin was claimed for the treatment of bacterial infections in animals (96CP2176298, 97MIP7) and it was applied for the prevention of bacterial infections in humans (96MI24). Pharmacokinetics and relative bioavailability of **7** were reported in Chinese healthy volunteers (99MI41). Solubilization (99MIP1) and application of **7** in papermaking process (98JAP(K)98/330205) were patented. Usage of **7** for the topical and/or local treatment of diseases caused by bacteria (01MIP16), and its nitrate salt (01MIP14) were patented. The accumulation of fluoroquinolones, including **7** and its 3-fluoromethyl derivative, into intact cell of *E. coli*, *S. aureus* and *Pseudomonas aeruginosa* was investigated (99MI11).

## IX. Pyrido[1,2-*a*]pyrazines and Their Benzologs

### A. STRUCTURE

#### 1. Thermodynamic Aspects

The lipophilicity ( $R_M$  value) and specific hydrophobic surface area of pyrido[1,2-*a*]pyrazinium-1-olates **342** and -olate **343**, and 1-(4-chlorophenyl)-1-hydroxy-1,2-dihydropyrazino[2,1-*a*]isoquinolinium salt (**344**) has been measured by reversed-phase thin-layer chromatography (98MI13). Partition coefficient ( $\log P$ ) of 9-bromo-5-[(*N*-phenylaminocarbonyl)-methyl]-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-dione was calculated to be 2.78 (97JMC4053).



Reversed-phase HPLC method was used for the assay and purity determination of **4** drug substance (97JC(A)233), for its determination in tablets, and its penultimate precursor **345**, together with two degradants **346** (98MI64, 98MI99). Sunepitron (**4**) was determined in biological fluids by HPLC–mass spectrometry (98JC(B)87). The absorption and metabolism of antianxiety drug candidate **4** in Long Evans rats and in cynomolgus monkeys were investigated by LC/MS/MS technique (97MI58, 97MI59).

A TLC and UV spectrophotometric assay was developed for determination of praziquantel (**9**) (99MI52). Praziquantel–erythrocyte interaction was studied by measuring partition coefficient of **9** between membrane and H<sub>2</sub>O, and also its hemolytic activity was determined (99MI49). Partition coefficient of **9** was measured at pH 7.4 between *n*-octanol and H<sub>2</sub>O (00MI6). Solubility properties of **9** and its enantiomers were investigated (98MI75). Dissolution properties of different praziquantel–polyvinylpyrrolidone formulations were determined (98MI20, 99CPB1629). Aqueous solubility of **9** was improved by forming inclusion complexes with  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins (99MI43). Physicochemical and spectroscopic properties of **9** were summarized (98MI70).

Enantiomers of praziquantel (**9**) were separated and they were determined in plasma samples and human serum (97AAC1256, 97JC(B)141, 97JC(B)307) on HPLC using a chiral column (98MI11). Enantiomers of **9** were separated by capillary electrophoresis using charged cyclodextrin (99EUP893453), and highly sulfated  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins (99MI39), by strong anion-exchange capillary electrochromatography with dynamically modified sulfated  $\beta$ -cyclodextrin (00MI54). Resolution of enantiomers of **9** was also achieved on chiral stationary phases (99JLC1813). Effect of the coating solvent on chiral recognition ability of enantiomers of **9** by coated chiral stationary phases was investigated (00MI13). Enantiomers of **9** and its *trans*-4-hydroxy metabolite determined in human plasma by cyclodextrin modified micellar electrokinetic chromatography (01MI12), and they were separated by chiral capillary electrophoretic method using sulfated  $\beta$ -cyclodextrin (01JLC1115).

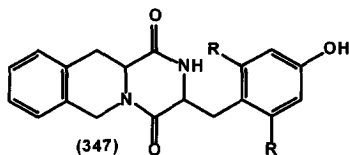
Adsorption stripping voltammetry was used for quantitative determination of **9** in tablets (97MI25). Praziquantel (**9**) was determined in biological fluids and different pharmaceutical formulations by HPLC (98JC(A)237), by UV spectrophotometric (97MI16), and by spectrofluorometric methods (98MI1). A sensitive polarographic determination of **9** in tablets after derivatization using Vilsmeier formylation was developed (01PHA146). Praziquantel was determined in human serum by voltammetric methods in tablets and biological fluids (01AF673, 01MI8). An ELISA method was developed for the determination of **9** in serum (01MI9). The related substances in **9** were determined by HPLC (97MI35). Stereoselective

metabolism of **9** was investigated by capillary electrophoresis and LC–MS (98JC(B)267). Organic solvent residue was determined in **9** by capillary gas chromatography (98MI23). Capillary electrophoresis–mass spectrometry and LC–MS coupling was used for the investigation of metabolites of **9** in human urine (00JC(B)221).

A related substance of quinapril, 3-methyl- $\alpha$ -(2-phenylethyl)-1,4-dioxo-1,3,4,6,11,11a-hexahydro-2H-pyrazino[1,2-*b*]isoquinoline-2-acetic acid, was determined by a HPLC method in drug substance (00MI55).

## 2. Theoretical Calculations

The conformational state of partially rigid tricyclic diketopiperazine **347** ( $R = \text{Me}$ ) was calculated by molecular dynamics and molecular mechanics (97MI12, 97MI21). Monte Carlo conformation analysis generated three low level clusters of conformers of **347** ( $R = \text{Me}$ ) (97MI21). *cis*-3,11a-H Derivative of diketopiperazine **347** ( $R = \text{H}$ ) was included in a series of opioid peptides, for which a relationship between structure and activity was studied (98MI57). 5-HT<sub>1A</sub>/ $\alpha$ -Adrenergic receptor affinities of a series of arylpiperazines, including 15 2-[ $\omega$ -(4-aryl-1-piperazinyl)alkyl]perhydropyrido[1,2-*a*]pyrazones, were analyzed by classical Hansch analysis, artificial neural networks, and computational simulation of ligand recognition (01JMC198). Physicochemical influence of the pharmacophore on the receptor affinity of these types of compounds was studied (01JMC186). Human intestinal absorption of **9** was predicted by using five Abraham descriptors (01JPS749).



## 3. IR Spectroscopy

Crystallinity of **9** in solid dispersions with polyethylene glycol (PEG 400) and urea was measured by IR and X-ray diffraction methods (00JPS79).

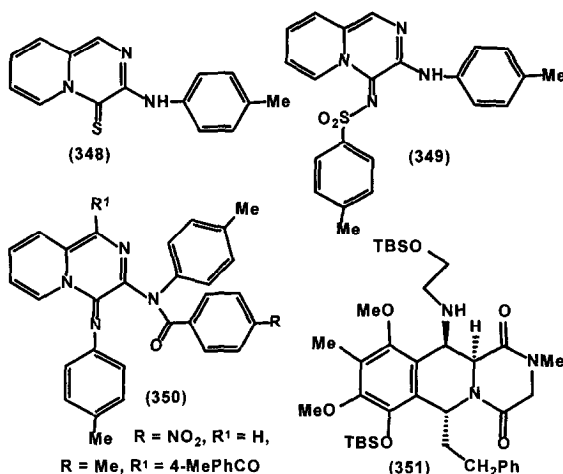
## 4. <sup>1</sup>H NMR Spectroscopy

Conformation analysis of 3-[(4-hydroxy-2,6-dimethylphenyl)methyl]-2,3,4,6,11,11a-hexahydro-1H-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**347**,  $R = \text{Me}$ ) was carried out in different solvents (in D<sub>2</sub>O at 300 K, in a 9:1 mixture of DMSO-*d*<sub>6</sub> and D<sub>2</sub>O at 278 K, in CD<sub>3</sub>OD at 220 K, in C<sub>6</sub>D<sub>6</sub> at

280 K, in  $\text{CD}_3\text{COCD}_3$  at 240 K), sometimes at different temperature (in  $\text{CDCl}_3$  at 216–303 K) by  $^1\text{H}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectra are dependent markedly on solution conditions, and suggest that there are different equilibrium mixtures of accessible conformers (97MI12).

### 5. X-ray Investigation

Structure of 4*H*-pyrido[1,2-*a*]pyrazines **348–350** was confirmed by X-ray investigations (99JPR332). The stereostructure of 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione **351** was determined by X-ray investigation (01TL543).



## B. REACTIVITY

### 1. Reduction, Hydrogenation

Racemic or optically active perhydropyrido[1,2-*a*]pyrazines were obtained by reduction of 9*aS*-perhydropyrido[1,2-*a*]pyrazin-4-one with LAH in  $\text{Et}_2\text{O}$  at room temperature (99H(51)2065) and by reduction of perhydropyrido[1,2-*a*]pyrazine-1,4-diones with LAH in boiling THF (97USP5703072, 00JAP(K)00/86659). Treatment of (9*aS*)-2-(*tert*-butoxycarbonyl)perhydropyrido[1,2-*a*]pyrazin-4-one with LAH in  $\text{Et}_2\text{O}$  afforded (9*aS*)-2-*tert*-butoxycarbonyl-1,6,7,8,9,9*a*-hexahydro-2*H*-pyrido[1,2-*a*]pyrazine (99H(51)2065).

Reduction of ethyl 3-[(2-*tert*-butoxycarbonyl)perhydropyrido[1,2-*a*]pyrazin-7-yl)methoxy]benzoate with LAH in THF at room temperature yielded

a  $\text{PhCH}_2\text{OH}$  derivative (99MIP9). A side chain cyano group was reduced with LAH to an aminomethyl group, which was alkylated with  $\text{Br}(\text{CH}_2)_4\text{Br}$  and 2-chloroethyl ether to afford a pyrrolidinomethyl and 4-morpholinyl-methyl derivatives of perhydropyrido[1,2-*a*]pyrazine, respectively.

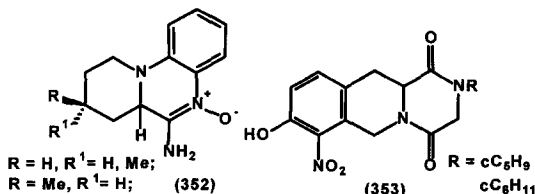
3-Benzyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines were obtained from 1-oxo derivatives by treatment with  $\text{NaBH}_4$  in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in boiling THF (00MIP6, 01USP6169086). The 3-unsubstituted derivatives were obtained from the above 3-benzyl derivatives with  $\text{NH}_4\text{OAc}$  in the presence of 10% Pd/C catalyst in boiling MeOH.

Reduction of a 7-(2-oxoethyl) derivative with  $\text{NaBH}_4$  in EtOH at room temperature gave 7-(2-hydroxyethyl)-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine (99MIP6). Reduction of 7-formyl-8-[(4-cyanophenyl)methoxy]-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with  $\text{NaBH}_4$  yielded a 7-hydroxymethyl derivative (98MIP7).

Methyl 2-substituted perhydropyrido[1,2-*a*]pyrazine-8-acetates were obtained by catalytic hydrogenation of 2-substituted 8-(methoxycarbonylmethylene)perhydropyrido[1,2-*a*]pyrazines over 10% Pd/C catalysts (00JAP(K)00/86659). A side chain 4-pyridyl group was hydrogenated over  $\text{PtO}_2$  catalysts to yield a 4-piperidyl derivative.

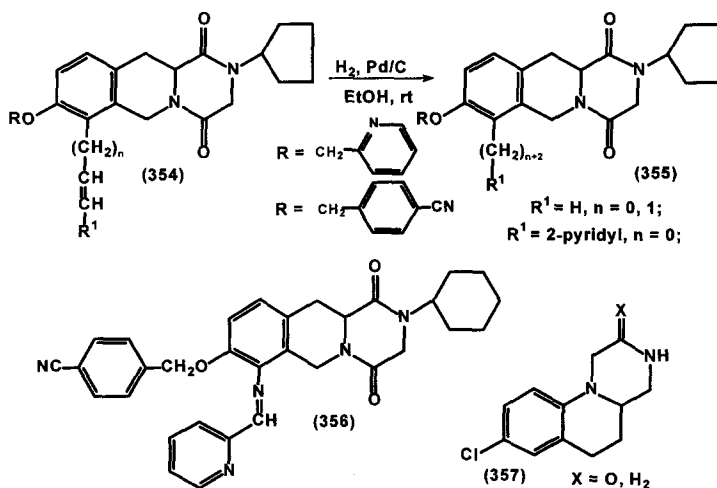
7-Aminomethyl-2-substituted perhydropyrido[1,2-*a*]pyrazines were obtained by catalytic hydrogenation of 7-azidomethyl derivatives over 5% Pd/C catalyst in a mixture of MeOH and EtOH (00MIP15), and over  $\text{PtO}_2$  in a mixture of EtOH and EtOAc (01MIP20). Catalytic hydrogenation of 2-(2-chloropyrimidin-4-yl)-, 2-(6-chloropyridazin-3-yl)- and 2-(2-nitro-5-fluorophenyl)perhydropyrido[1,2-*a*]pyrazines over 10% Pd/C afforded 2-(4-pyrimidinyl), 2-(3-pyridazinyl) and 2-(2-amino-5-fluorophenyl) derivatives (01EUP1074257). Boiling 2-(4-methylthio-5-fluoro-2-pyrimidyl)perhydropyrido[1,2-*a*]pyrazine in EtOH in the presence of an excess of Raney Ni gave a 2-(5-fluoro-2-pyrimidyl) derivative. Catalytic hydrogenation of a 7-styryl derivative of perhydropyrido[1,2-*a*]pyrazines over 80% Pd/C in  $\text{H}_2\text{O}$  yielded a 7-(2-phenylethyl) derivative (01EUP1074257).

Catalytic hydrogenation of 5-oxy-7,8,9,10-tetrahydro-6*aH*-pyrido[1,2-*a*]quinoxalin-6-ylamines **352** over Pearlman's catalyst under 5 atm of  $\text{H}_2$  in MeOH for 5–7 days at room temperature gave 6,6*a*,7,8,9,10-hexahydro-5*H*-pyrido[1,2-*a*]quinoxalines (01EJOC987).



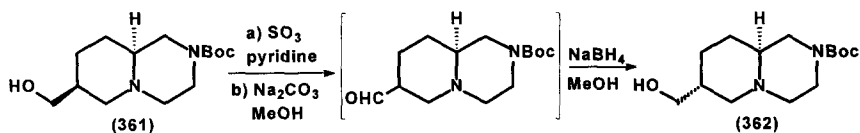
2-(5-Amino-2-methoxyphenyl)perhydropyrido[1,2-*a*]pyrazine was prepared from 2-(5-nitro-2-methoxyphenyl)-3-one derivative by catalytic hydrogenation over Pd/C catalyst in EtOH, followed by the reduction of 3-oxo group by treatment with  $\text{BF}_3 \cdot \text{THF}$  complex in boiling THF (99MIP10). Catalytic hydrogenation of 2-[4-(3-nitrophenyl)piperazin-1-yl]butyl]perhydropyrido[1,2-*a*]pyrazine-1,4-dione over Pd/C in methanol yielded an amino derivative (01JMC186). Nitro group of 2-(4-nitrobenzoyl)-1,2,3,6,7,11*a*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one was reduced to an amino group with Fe in AcOH (97MI9). Catalytic hydrogenation of 8-hydroxy-7-nitro-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones (**353**) over Pd/C catalyst in EtOH at 50°C afforded 7-amino derivatives (98MIP7). Reduction of 8-nitro-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with 1M  $\text{BF}_3 \cdot \text{THF}$  complex in boiling THF gave 8-nitro-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline (97MIP4). The nitro group was reduced to an amino group by catalytic hydrogenation over 5% Pd/C catalyst in aqueous MeOH in the presence of conc. HCl under 50 psi of hydrogen.

The side chain C=C double bond of 2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones **354** was saturated by catalytic hydrogenation over Pd/C catalysts in EtOH to give **355** (98MIP7). 7-(2-Pyridylmethyl)amino derivative was obtained by reduction of 7-[(2-pyridylmethylene)amino]-2,3,11,11*a*-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**356**) with  $\text{NaBH}_4$  in EtOH at ambient temperature for 24 h.





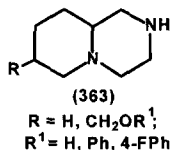
with  $\text{NaBH}_4$  (98BMCL725, 99MIP9). Oxidation of a 7-hydroxy-methyl-perhydropyrido[1,2-*a*]pyrazine with  $\text{Pr}_4\text{NRuO}_4$  in the presence of *N*-methylmorpholine-*N*-oxide in  $\text{CH}_2\text{Cl}_2$  yielded a 7-formyl derivative (01EUP1074257). Swern oxidation of 7-[(4-fluorophenyl)hydroxymethyl]-2-(2-pyrimidyl)perhydropyrido[1,2-*a*]pyrazines yielded 7-(4-fluorobenzoyl) derivatives (01EUP1074257). Swern oxidation of 7-hydroxyethyl-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazines yielded 7-formyl derivatives (99MIP6, 01EUP1074257).



### 3. Reactivity of Ring Nitrogen Atom

2-Unsubstituted perhydropyrido[1,2-*a*]pyrazines were N-alkylated with alkyl mesylates (00JAP(K)00/86659), alkyl halogenides (00JAP(K)00/86659) and with a bromomethyl ketone (01MIP3), and were N-acylated with di-*tert*-butyl dicarbonate (98BMCL725, 01MIP20), and with *tert*-butoxycarbonyl chloride (00JAP(K)00/86659). Perhydropyrido[1,2-*a*]pyrazine-1,4-diones were N-alkylated with  $\text{Br}(\text{CH}_2)_4\text{Br}$  and 3-(4-aryl-1-piperazinyl)propyl chlorides in DMF in the presence of NaH (60%) at  $110^\circ\text{C}$  (01JMC186).

7-Substituted perhydropyrido[1,2-*a*]pyrazines were reacted with 2-fluorobenzohydroximinoyl chlorides in the presence of DBU in  $\text{CHCl}_3$  to yield a isomeric mixture of 7-substituted 2-[(hydroxyimino)phenylmethyl]-perhydropyrido[1,2-*a*]pyrazines (99MIP9).

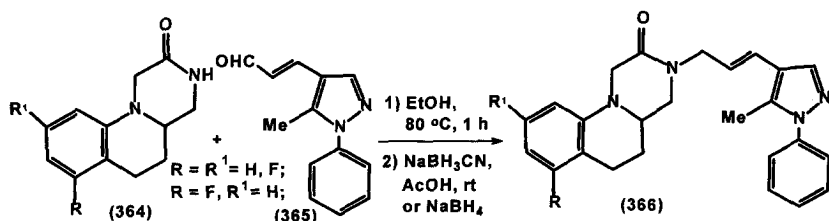


N-(Het)arylation of optically active and racemic perhydropyrido[1,2-*a*]pyrazines **363** has been carried out with 2,5-difluorobenzonitrile, 4-fluoro- and 2,5-difluoronitrobenzene in DMSO in the presence of  $\text{Na}_2\text{CO}_3$  (01EUP1074257), with 8,11-dichlorodibenzo-[*b,f*]-1,4-oxazepine in boiling MeCN overnight in the presence of *i*- $\text{Pr}_2\text{EtN}$  (97USP5703072), with 2-chloro- and 2,4-dichloropyrimidines (98BMCL725, 01EUP1074257), with 3,6-dichloropyridazine, 2-chloropyrazines in  $\text{H}_2\text{O}$  in the presence of  $\text{Na}_2\text{CO}_3$  (01EUP1074257), with 2-halopyridines in boiling *i*-amyl alcohol

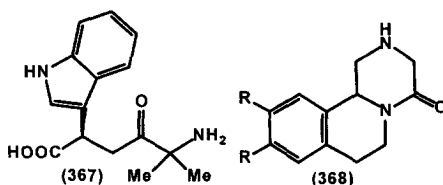


in the presence of  $\text{Na}_2\text{CO}_3$  (98BMCL725, 01EUP1074257), with 2,6-dimethoxypyridine in THF in the presence of BuLi (01EUP1074257), with 1-acetyl-3-indolone in boiling toluene in the presence of *p*TSA (99MIP8, 00MIP4, 01EUP1074257, 01USP6251893), with 3-chloro-1-(4-methylphenylsulfonyl)indazole at 120 °C (99MIP8, 01USP6251893), with 6-bromo-1-triisopropylsilylindole in xylene at 120 °C in the presence of NaOt-Bu, Pd/OAc<sub>2</sub> and P(*t*-Bu)<sub>3</sub> (01MIP5), with 2-chloro-4-aminoquinazoline in isoamyl alcohol at 140 °C (01MIP20), with 2-methoxy-1-[1-(1-methylcyclooctyl)-4-piperazinyl]-1*H*-benzimidazole (01JAP(K)01/213878), and with 3-chlorobenzo[*d*]isoxazole in the presence of DBU in anhydrous pyridine at 90 °C (99MIP9).

3-[(4-Phthalimidobutyl)-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline was obtained in the reaction of 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline and *N*-(4-bromobutyl)phthalimide in boiling MeCN in the presence of  $\text{K}_2\text{CO}_3$  (97MIP12). 2,3,4,4*a*,6,7-Hexahydro-1*H*-pyrazino[1,2-*a*]quinolines were N-alkylated with 3-dimethylaminomethyl-1*H*-pyrrolo[2,3-*b*]pyridine and a mixture of 1*H*-pyrrolo[2,3-*b*]pyridine and 37% aqueous  $\text{H}_2\text{CO}$  in aqueous AcOH in the presence of NaOAc (96USP5576319). 3-[3-Substituted 2-propen-1-yl]-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines **366** were obtained in the reaction of 3-unsubstituted derivatives **364** and 3-substituted 2-*trans*-propenal **365**, and the following treatment of the reaction mixture with  $\text{NaBH}_3\text{CN}$  and  $\text{NaBH}_4$  (00MIP6, 01USP6169086).



7-[(2-Naphthylsulfonyl)aminomethyl]perhydropyrido[1,2-*a*]pyrazine was N(2)-alkylated with 1,2,3,4-tetrahydro-2-naphthoic acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide in  $\text{CH}_2\text{Cl}_2$ , then acyl group was reduced with  $\text{BH}_3 \cdot \text{THF}$  in boiling THF (01MIP20). Optically active 3-substituted perhydropyrido[1,2-*a*]pyrazine-1,4-diones were N-acylated with 4-(*tert*-butyl)benzene sulfonyl chloride and 3-methyl-1,2,3,4-tetrahydro-8-quinoline sulfonyl chloride in the presence of  $(\text{Me}_3\text{Si})_2\text{NLi}$  in THF at room temperature (01MIP18). Treatment of *trans*-7-(hydroxymethyl)perhydropyrido[1,2-*a*]pyrazine with 2 equiv. of 1-naphthalene sulfonyl chloride in a 1:1 mixture of pyridine and  $\text{CH}_2\text{Cl}_2$  at room temperature for 22 h yielded 7-chloromethyl-2-(1-naphthylsulfonyl) derivative (01MIP20).



4a-Methyl-1,2,3,4,4a,5-hexahydro-10H-pyrazino[1,2-b]isoquinolin-10-one was N-acylated with carboxylic acid **367** in the presence of  $\text{NEt}_3$  and 1-propanephosphonic acid cyclic anhydride in EtOAc at room temperature (98MIP18). 1,2,3,6,7,11b-Hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-ones **368** were N-acylated with different acyl chlorides (96MI8, 97MI9, 98MI88, 98T7395, 00MI12), and thioacyl chlorides (96MI8). Reaction of **368** ( $\text{R} = \text{H}$ ) and 2-hydroxyethyl chloride gave 2-(2-hydroxyethyl) derivative (96MI8). Reaction of **368** ( $\text{R} = \text{H}$ ) and methylene and trimethylene bromides, furthermore oxalyl and adipoyl chlorides afforded bis derivatives (96MI8). 7-Aryl-5-oxo-1,2,3,5-tetrahydropyrido[1,2,3-de]quinoxaline-6-carboxamides were N-alkylated and N-acylated (01MIP12).

For further examples see Section IX.B.1.

#### 4. Reactivity of Substituents Attached to Ring Nitrogen Atom

Amino group of 2-(5-amino-2-methoxyphenyl)perhydropyrido[1,2-a]pyrazine was acylated with 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride in the presence of  $\text{NEt}_3$  in  $\text{CH}_2\text{Cl}_2$  (99MIP10). Acylation of 2{4-[(3-aminophenyl)piperazin-1-yl]butyl}perhydropyrido[1,2-a]pyrazine-1,4-dione with isobutyryl chloride in pyridine gave an 3-isobutyrylamidophenyl derivative (01JMC186). The piperidino nitrogen of 2-(4-piperidyl)perhydropyrido[2,1-a]pyrazine was acylated (98MIP2, 99JAP(K)99/222431).

Perhydropyrido[1,2-a]pyrazines were obtained from 2-*tert*-butoxycarbonyl derivatives by treatment with HCl gas in  $\text{CHCl}_3$  (98BMCL725, 01EUP1074257) in  $\text{Et}_2\text{O}$  (99MIP9), and with TFA (00JAP(K)00/86659, 01EUP1074257, 01MIP20). (9a*S*)-Perhydropyrido[1,2-a]pyrazin-4-one was obtained from its 2-(*tert*-butoxycarbonyl) derivative by stirring in acidified MeOH for 30 min at room temperature (99H(51)2065).

2-(Benzo[d]isoxazol-3-yl)perhydropyrido[1,2-a]pyrazines were obtained by the cyclization of 2-[(hydroxyimino)phenylmethyl]pyrido[1,2-a]pyrazines on the action of NaH in THF at 90°C for 18 h (99MIP9).

Amino group of 3-(4-aminobutyl)-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoline, prepared from 3-[4-phthalimidobutyl] derivative by treatment with  $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$  in boiling EtOH, was acylated with 2-fluorencarbonyl chloride in the presence of  $\text{NEt}_3$  in  $\text{CHCl}_3$  (97MIP12).

Triisopropylsilyl group of 2-[1-triisopropylsilyl-1*H*-indol-6-yl]perhydropyrido[1,2-*a*]pyrazine was removed by treatment with Bu<sub>4</sub>NF in THF (01MIP5).

1-Acetyl-3-(perhydropyrido[1,2-*a*]pyrazin-2-yl)-1*H*-indole was deacetylated in boiling MeOH in the presence of NaOH, and the product, 3-(perhydropyrido[1,2-*a*]pyrazin-2-yl)-1*H*-indole was N-acylated with different arylsulfonyl chloride in THF at 0 °C in the presence of (Me<sub>3</sub>Si)<sub>2</sub>NNa (99MIP12, 01USP6251893)).

Bromo atom of 2-(4-bromobutyl)perhydropyrido[1,2-*a*]pyrazine-1,4-diones was substituted by 1-arylpiperazines in boiling MeCN in the presence of NEt<sub>3</sub> (01JMC186). Halogen atom of 3-{3-[1-(6-halo-2-amino-4-pyrimidinyl)-5-methyl-4-pyrazinyl]-2-propenyl}-7,9-difluoro-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines was changed for substituted amino groups with amines (00MIP6). Reaction of 2-(2-chloroethyl)-1,2,3,6,7,11*a*-hexahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-one, prepared from 2-(2-hydroxyethyl) derivative with SOCl<sub>2</sub>, and piperidine yielded 2-(2-piperidinoethyl) derivative (96MI8).

Ester group of 1-(ethoxycarbonylmethyl)-7-aryl-5-oxo-1,2,3,5-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxamides was hydrolyzed and the 1-carboxymethyl moiety was converted to an aminocarbonylmethyl group with 1-methylpiperazine (01MIP12). Bromo atom of 1-(2-bromoacetyl) derivatives was substituted by different amines. An amino group in the side chain attached to the position 1 of 7-aryl-5-oxo-1,2,3,5-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxamides was acylated, and *tert*-butoxycarbonyl protecting group of amino group was eliminated.

For some example see Section IX.B.1.

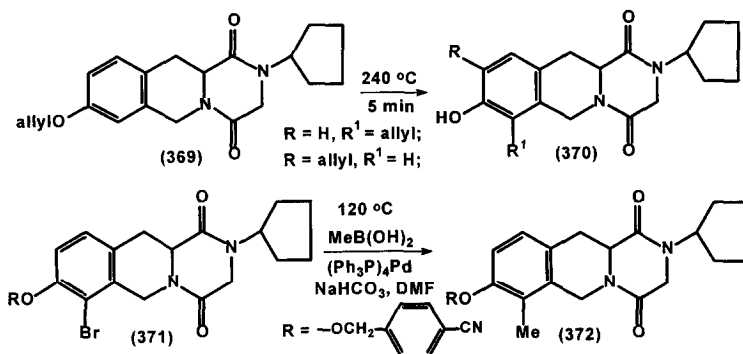
### 5. Reactivity of Ring Carbon Atoms

8-(Methoxycarbonylmethylene) derivatives were prepared in the reaction of 2-(*tert*-butoxycarbonyl)perhydropyrido[1,2-*a*]pyrazin-8-ones and (EtO)<sub>2</sub>P(O)CH<sub>2</sub>COOMe in the presence of NaH in THF at room temperature (00JAP(K)00/86659). Wittig reaction of a 7-formylperhydropyrido[1,2-*a*]pyrazine with PhCH<sub>2</sub>PPh<sub>3</sub>Cl in the presence of BuLi in THF at -78 °C gave a 7-styryl derivative (01EUP1074257).

7-Chloro-, 7-bromo- and 7-iodo derivatives were prepared from 2-cycloalkyl-8-hydroxy-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones by treatment with NCS and NBS in DMF at 70 °C for 24 h, with ICl in diluted HCl at 90 °C for 16 h, respectively (98MIP7).

Nitration of 2-cyclohexyl-8-hydroxy-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with 70% HNO<sub>3</sub> at room temperature for 30 min afforded an 1 : 1 mixture of 7- and 9-nitro derivatives (98MIP7).

Heating 8-(prop-2-enyl)-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione **369** afforded a mixture of 7- and 9-(prop-2-enyl) derivatives **370** (98MIP7).



Reaction of 7-bromo-8-(*tert*-butyldimethylsilyloxy)-2-cyclopentyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with vinyltributylstannane in boiling toluene in the presence of (Ph<sub>3</sub>P)<sub>4</sub>Pd gave 7-vinyl derivative (98MIP7). Reaction of 7-bromo-8-[(4-cyanophenyl)methoxy]-2-cyclopentyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with 2-trimethylstannylthiophene or with other similar reagents in the presence of (Ph<sub>3</sub>P)<sub>4</sub>Pd in DMF gave 7-hetaryl derivatives (2-, 3-thienyl, 2-furyl, *N*-methyl-2-pyrrolyl, 2-thiazolyl, 5-methyl-2-thienyl). 7-Methyl derivative **372** was prepared from 7-bromo derivative **371** with MeB(OH)<sub>2</sub> in the presence of NaHCO<sub>3</sub> and (Ph<sub>3</sub>P)<sub>4</sub>Pd in DMF at 120 °C. 7-Cyano derivative was prepared from 2-cyclopentyl-8-hydroxy-7-iodo-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione by treatment with KCN in the presence of 18-crown-6 and (Ph<sub>3</sub>P)<sub>4</sub>Pd in boiling THF overnight.

Reaction of 10-bromo-*N*,1,3-trimethyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamide with 2,6-dimethyl-4-(tributylstannyl)-pyridine in the presence of (Ph<sub>3</sub>P)<sub>2</sub>Pd(II)Cl in boiling toluene gave 10-(2,6-dimethyl-4-pyridyl) derivative (00MIP10).

2-(4-Nitrophenyl)-1*H*-pyrido[1,2,3-*de*]quinoxalinium bromide (**296**, X = NH, R = NO<sub>2</sub>) reacted with a heterocyclic quaternary salt **254** in position 7 to give a monomethine cyanine dye **257** (X = NH, R = NO<sub>2</sub>) (98MI45).

1,2,3,6,7,11*a*-Hexahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-thione and its 2-thioacyl derivatives were prepared from 4-one and 2-acyl-4-ones derivatives, respectively (96MI8).

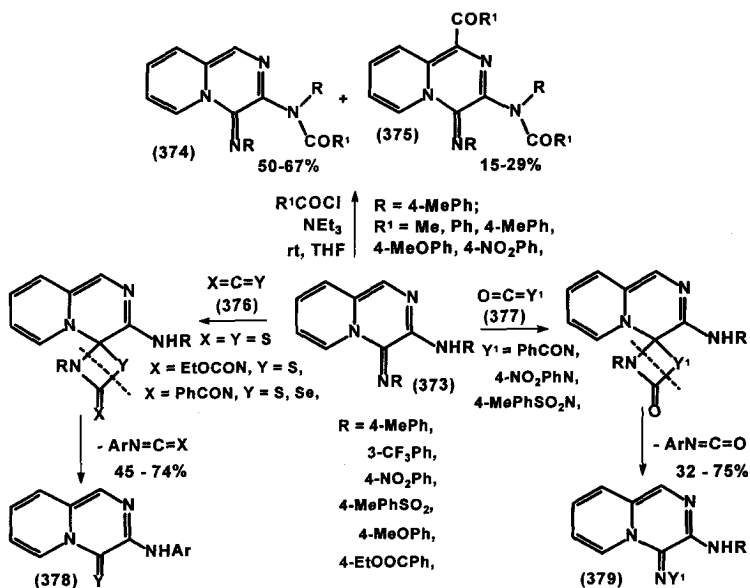
Vilsmeier formylation of praziquantel (**9**) with DMF-POCl<sub>3</sub> at 60°C for 5 h gave 2-cyclohexylcarbonyl-3-dimethyliminiummethylene-4-chloro-1,6,7,11*b*-tetrahydro-2*H*-pyrazino[2,1-*a*]isoquinoline salt (01PHA146).

7-Aryl-5-oxo-1,2,3,5-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboximides were prepared from 7-chloro derivatives and arylboronic acids in the presence of Na<sub>2</sub>CO<sub>3</sub>, diphenylphosphinated divinylbenzene-crosslinked polystyrene and Pd(PPh<sub>3</sub>)<sub>4</sub> catalyst. 7-Chloro derivatives were obtained from 7-hydroxy derivatives by heating in POCl<sub>3</sub> at 50°C for 3 h (01MIP12).

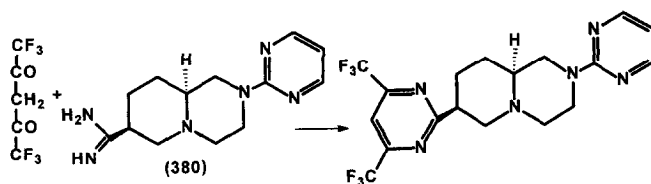
For further example see Section IX.B.6.

#### 6. Reactivity of Substituents Attached to Ring Carbon Atoms

Acylation of 3-arylamino-4-arylimino-4*H*-pyrido[1,2-*a*]pyrazines (**373**) with acyl chlorides afforded mixtures of mono- and bisacylated derivatives **374** and **375** (99JPR332). Acetyl chloride gave only monoacylated product **374** (R = 4-MePh, R<sup>1</sup> = Me). Bis-acylated derivative **375** (R = 4-MePh, R<sup>1</sup> = Me) was obtained in 68% yield in boiling toluene. Reaction of **373** with dienophiles **376** and **377** gave 4-thiono and 4-seleno derivatives of 4*H*-pyrido[1,2-*a*]pyrazines **378** (Y = S, Se) and 4-imino-4*H*-pyrido[1,2-*a*]pyrazines **379**, respectively (99JPR332).



A metabolite **380** of sunepitron (**4**) was derivatized by the reaction with hexafluoroacetylacetone (97MI59).



Hydroxy group of *trans*-7,9a-H-7-( $\omega$ -hydroxyalkyl)-2-(2-pyrimidyl)perhydropyrido[1,2-*a*]pyrazine was arylated with 5-methylthio-2-methyl-2*H*-[1,2,4]thiazin-3-one in 1,2-dimethoxyethane in the presence of a base (NaH or *t*-BuOK) (99MIP6). 7-(2-Oxoethyl) derivative was prepared from 7-formyl-2-(2-pyrimidyl)perhydropyrido[1,2-*a*]pyrazine by the treatment with  $\text{MeOCH}_2\text{P(Ph)}_3\text{Cl}$  in the presence of *i*-Pr<sub>2</sub>NH in THF at 0°C, than with BuLi at room temperature (99MIP6).

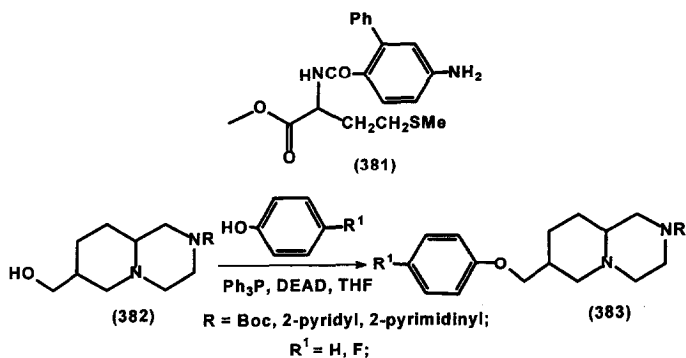
Reaction of a 7-formyl group in perhydropyrido[1,2-*a*]pyrazine with 4-FPhMgBr in THF at -10°C yielded 7-[4-fluorophenyl]hydroxymethyl] derivative (01EUP1074257). Reaction of a 7-mesyloxymethyl group in perhydropyrido[1,2-*a*]pyrazine with NaCN in DMF at 110°C gave a 7-cyanomethyl derivative, which was converted into a 2-oxoethyl group by treatment first with DIBAL at room temperature for 2 h, than at 50°C for 1 h, than with 2 M HCl at room temperature. 2-Oxoethyl group was reacted with 4-FPhMgBr in THF at -10°C to yield a 7-[2-(4-fluorophenyl)-2-hydroxyethyl] derivative (01EUP1074257). 7-Cyanomethyl derivative was reacted with 4FPhMgBr in the presence of Cu(I)Br in boiling THF for 48 h, then the reaction mixture was treated with 15% aqueous H<sub>2</sub>SO<sub>4</sub> under reflux for 24 h gave a 7-[2-(4-fluorophenyl)-2-oxoethyl] derivative.

A side chain 7-[3-(mesyloxymethyl)phenoxy]methyl group of a perhydropyrido[1,2-*a*]pyrazine was converted to 7-[3-(aminomethyl)phenoxy]-methyl groups by the treatment with different amines (99MIP9).

7-Mesyloxymethyl-2-substituted perhydropyrido[1,2-*a*]pyrazines were prepared from 7-hydroxymethyl derivatives with  $\text{MeSO}_2\text{Cl}$  in the presence of NEt<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 0°C (00MIP15, 01EUP1074257). 7-Mesyloxymethyl (00MIP15), 7-chloromethyl (01MIP20), and 7-tosyloxymethyl (01MIP20) derivatives were converted into 7-azidomethyl derivatives by treatment with NaN<sub>3</sub> in DMF at 50–75°C. A 7-mesyloxymethyl group was reacted with 2-benzoxazoline, 5-fluoroindole, oxindole, and 2-methylbenzimidazoles in DMF in the presence of NaH (60%) (01EUP1074257). 5-Fluoroindole was treated with EtMgBr in benzene, then a 7-mesyloxymethylperhydropyrido[1,2-*a*]pyrazine was added to the reaction mixture at room temperature yielded a 7-[(5-fluoro-1*H*-indol-3-yl)methyl] derivative, which was N-methylated in a separate step by treatment with MeI in DMF in the presence of NaH at 50°C (01EUP1074257).

Amino group of 7-aminomethyl-2-substituted perhydropyrido[1,2-*a*]pyrazines were reacted with 2-bromopyridine and 2-chloropyrimidines to give 7-(hetarylamino)methyl derivatives in the presence of  $\text{Na}_2\text{CO}_3$  in DMF at 100–120°C for 18 h in 13–51% yields (00MIP15). An aminomethyl group of 2-substituted perhydropyrido[1,2-*a*]pyrazines was acylated with 2-naphthylsulfonyl chloride in  $\text{CH}_2\text{Cl}_2$  in the presence of pyridine, it was reacted with different hetaryl halogenides in an alcohol (isoamylalcohol, 1-pentanol) at 140°C, with 3-bromoquinoline in the presence of  $\text{NaOt-Bu}$ , tris(dibenzylideneacetone)dipalladium(0)–chloroform adduct, and (*S*)-2,2'-bis(diphenylphosino)-1,1'-binaphthyl in toluene at 70°C (01MIP20). An 7-aminomethyl group was acylated with 1,2,3,4-tetrahydro-2-naphthoic acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide in  $\text{CH}_2\text{Cl}_2$ , and the amide was reduced to 7-[(1,2,3,4-tetrahydro-2-naphthyl)methyl]aminomethyl group with  $\text{BH}_3 \cdot \text{THF}$  in boiling THF (01MIP20). Reaction of a 7-aminomethyl group with 3-quinolinecarboxaldehyde in EtOH in the presence of AcOH and  $\text{NaBH}_3\text{CN}$  gave 7-[(3-quinolinylmethyl)aminomethyl] derivative (01MIP20).

Amine bound to a Wang-polystyrene resin **381** was acylated with 4-oxo-4*H*-pyrido[1,2-*a*]pyrazine-3-carboxylic acid in the presence of bromotrispyrrolidinophosphonium hexafluorophosphate and *i*-Pr<sub>2</sub>NEt in *N*-methylpyrrolidone (98MIP16). 1-(4-Cyclohexyl-4-*tert*-butylaminocarbonyl-1-piperidyl)-2-(4-fluorophenyl)ethylamine was acylated with perhydropyrido[1,2-*a*]pyrazine-3-carboxylic acid (01MIP19). An amino group of a macrocyclic compound attached to a solid support was acylated with 3-methyl-9-fluoro-10-(4-methylpiperazinyl)-7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylic acid in DMF in the presence of *i*-Pr<sub>2</sub>NEt, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, and 2,4,6-collidine (01MIP8).

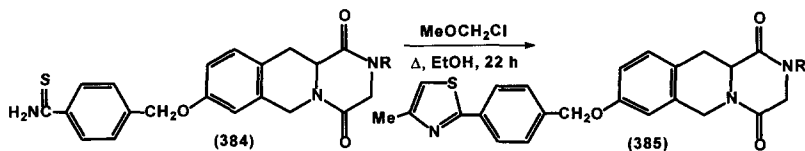


Hydroxyl group of 7-hydroxymethylperhydropyrido[1,2-*a*]pyrazines **382** was arylated by Mitsunobu coupling with phenols and 4-fluorothiophenol

to give 7-aryloxymethyl **383** and 7-(4-fluorophenylsulfanyl)methyl derivatives (98BMCL725, 99MIP9, 01EUP1074257). 7-Aryloxymethyl derivatives were also prepared in the reaction of 7-(mesyloxy)methyl derivatives and phenols in DMF in the presence of NaH (01EUP1074257).

Hydroxy group of 8-hydroxy-3-(4-methoxyphenylmethyl)-2-[4-(1-*tert*-butoxycarbonyl-4-piperidinyl)butyl]perhydropyrido[1,2-*a*]pyrazine was alkylated with *tert*-butyl chloroacetate (00JAP(K)00/86659).

Hydroxy group of 8-hydroxy-2-cycloalkyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones was alkylated with allyl bromide, 2-(bromodifluoromethyl)pyridines, 1-(bromodifluoromethyl)- and 1-(bromomethyl)benzenes, halomethyl derivatives of different heterocycles (pyridine, pyrazine, pyrazole, pyrrole, thiazole, thiophene) in the presence of  $\text{Cs}_2\text{CO}_3$  or  $\text{K}_2\text{CO}_3$  (98MIP7). Hydroxy group of 8-hydroxy-2-cyclopentyl-7-bromo-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione was silylated with *t*-BuMe<sub>2</sub>SiCl in DMF in the presence of imidazole at ambient temperature (98MIP7). 2-Cyclopentyl-7-ethyl-8-hydroxy-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione was recovered from 8-(*tert*-butyldimethylsilyloxy) derivative by treatment of 1 M  $\text{Bu}_4\text{NF}$  in THF.



8-[(4-Aminothiobenzoyl)phenyl]methoxy derivative **384** was obtained from 8-[(4-cyanophenyl)methoxy]-2-cyclohexyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione by treatment with  $(\text{EtO})_2\text{P}(\text{S})\text{SH}$  and one drop of  $\text{H}_2\text{O}$  at room temperature for 17 h, then followed by addition of more  $\text{H}_2\text{O}$  (98MIP7). Reaction of 8-[(4-aminothiobenzoyl)phenyl]methoxy derivative **384** and  $\text{MeCOCH}_2\text{Cl}$  yielded 8-[(4-(4-methylthiazol-2-yl)phenyl)methoxy] derivative **385**. 7-Bromomethyl derivative was prepared from the 8-hydroxymethyl-8-[(4-cyanophenyl)methoxy]-2-cyclopentyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with  $\text{PBr}_3$  in  $\text{CH}_2\text{Cl}_2$  at room temperature. 7-[(1-Pyrazolyl)methyl] derivative was obtained from 7-bromomethyl derivative by treatment with pyrazole in the presence of NaH in DMF at  $50^\circ\text{C}$ .

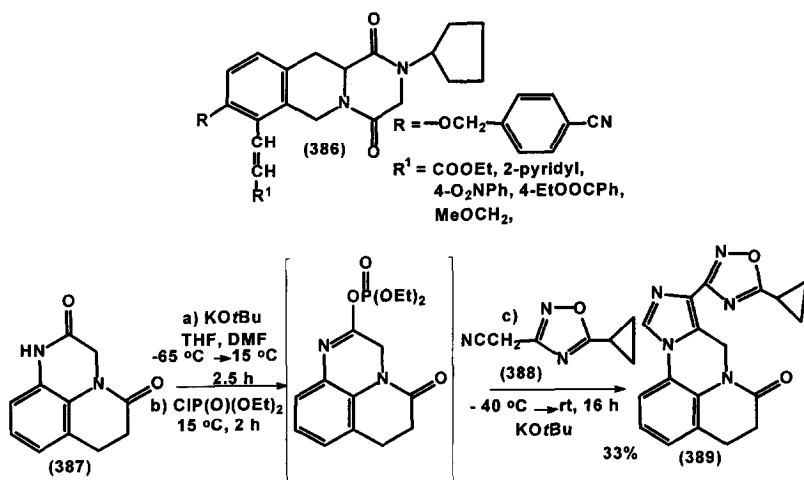
3-[ $\omega$ -(4-Methyltritylamino)alkyl]-2-substituted perhydropyrido[1,2-*a*]pyrazine-1,4-diones were deprotected by treatment with 1% TFA in  $\text{CH}_2\text{Cl}_2$  to give 3-( $\omega$ -aminoalkyl) derivatives. Amino group was reacted with *N,N'*-bis(*tert*-butoxycarbonyl)-*N''*-(trifluoromethanesulfonyl)guanidine in  $\text{CH}_2\text{Cl}_2$  in the presence of  $\text{NEt}_3$ . The formed *N,N'*-(di-*tert*-butoxycarbonyl)guanidine group was converted to a guanidine moiety with 1 : 1 mixture



of TFA and  $\text{CH}_2\text{Cl}_2$  and with 3N HCl in EtOAc (01MIP18). Treatment of 3-[[3-(*N*<sup>γ</sup>-4-methoxy-2,3,6-trimethylbenzenesulfonyl)guanidine]propyl]-2-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-8-methylperhydropyrido[1,2-*a*]pyrazine-1,4-dione with 1:1 mixture of TFA and  $\text{CH}_2\text{Cl}_2$  yielded 3-guanidinopropyl derivative.

Amino group of 7-amino-2-cycloalkyl-8-hydroxy-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones was acylated with acyl chlorides and  $\text{MeSO}_2\text{Cl}$  in  $\text{CH}_2\text{Cl}_2$  in the presence of  $\text{NEt}_3$ , and it was condensed with 4-dimethylaminobenzaldehyde, pyridine-2-carboxaldehyde, and 1-methylimidazole-2-carboxaldehyde to give the appropriate Schiff base (98MIP7). Amino group of 8-amino-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline dihydrochloride was acylated with *S*-methyl-2-thiophenethiocarboximide hydroiodide in DMSO in the presence of pyridine at 50 °C to give amidine **260** ( $\text{X}=\text{NH}$ ) (97MIP4). Amino group of 2-(4-aminobenzoyl)-1,2,3,6,7,11*a*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one was reacted with isothiocyanates, acyl chlorides, and it was involved in diazonium coupling (97MI9). Chloro atom of 2-[4-(2-chloroacetamido)-benzoyl]-1,2,3,6,7,11*a*-hexahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-one was substituted with amines (97MI9).

Treatment of 8-[(4-cyanophenyl)methoxy]-7-formyl-2-cyclopentyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione with  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$  and NaH in THF at 40 °C overnight, or with (2-pyridylmethyl)-, 4-[(ethoxycarbonyl)benzyl]-, (4-nitrobenzyl)-, and (methoxymethyl)triphenylphosphonium halogenide in the presence of KH in THF at room temperature gave 7-ethylene derivatives **386** (98MIP7).



Tetracyclic derivative **389** was obtained from 1,2,3,5,6,7-hexahydropyr-ido[1,2,3-*de*]quinoxaline-2,5-dione (**387**) by treatment with  $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$  in the presence of  $\text{KO}t\text{-Bu}$ , then with isocyanide **388** in the presence of an other portion of  $\text{KO}t\text{-Bu}$  (96JMC4654).

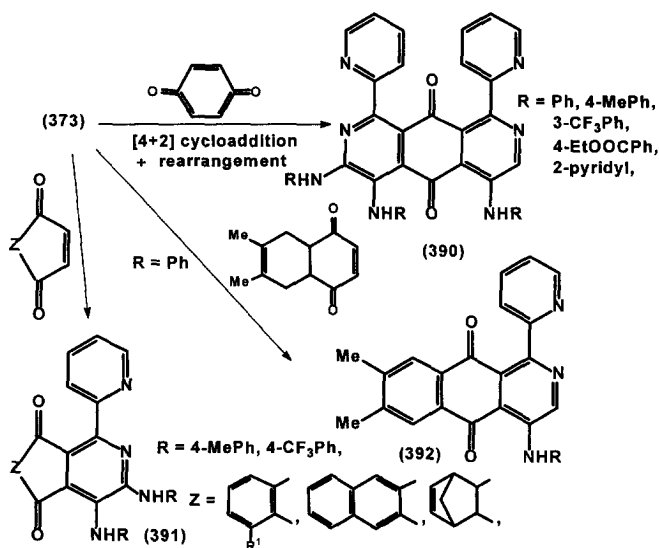
A side chain carboxyl group in perhydropyrido[1,2-*a*]pyrazines was obtained from an ester group by acidic or alkalic hydrolysis. A side chain carboxyl group was converted into a carboxamide group by the treatment with an amine in the presence of 1-hydroxybenzotriazole (00JAP(K)00/86659).

Ethyl 1-substituted 7-hydroxy-5-oxo-1,2,3,5-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylates were reacted with *N*-{[3,5-bis(trifluoromethyl)-phenyl]methyl}methylamine to yield carboxamides (01MIP12).

### 7. Ring Transformations

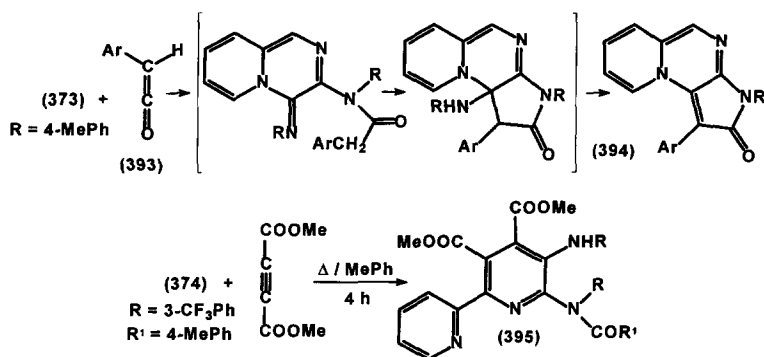
Different azanthraquinones **390–392** were prepared from 3-amino-4-imino-4*H*-pyrido[1,2-*a*]pyrazines **373** with 1,4-quinones in one pot reactions via [4+2] cycloaddition and the subsequent ring transformation (Scheme 9) (97T5455).

Reaction of 3-(4-methylphenylamino)-4-(4-methylphenylimino)-4*H*-pyrido[1,2-*a*]pyrazine (**373**,  $\text{R} = 4\text{-MePh}$ ) with ketenes **393**, prepared *in situ* from the appropriate acetyl chloride with  $\text{NEt}_3$ , yielded tricyclic derivatives



Scheme 9

**394** (99JPR332). Pyridine-3,4-dicarboxylates **395** were obtained in the reaction of 4*H*-pyrido[1,2-*a*]pyrazines **374** with DMAD.



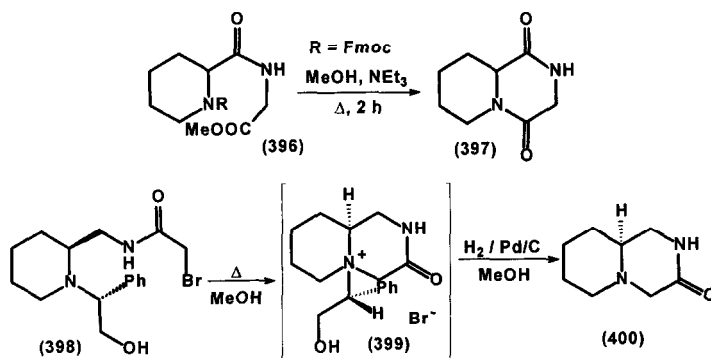
## 8. Miscellaneous

Racemic mixture of *trans*-2-(2-pyrimidyl)- and 2-*tert*-butoxycarbonyl-7-(hydroxymethyl)perhydropyrido[1,2-*a*]pyrazines were resolved using either L-(+) or D-(-)-tartaric acid, into optically active enantiomers with an optical purity of at least 99.7% (98BMCL725, 98MIP1). Separation of enantiomers of *trans*-7,9*a*-H-7-{2-[(2-methyl-3-oxo-2*H*-1,2,4-triazin-5-yl)oxy]ethyl}-2-(2-pyrimidyl)perhydropyrido[1,2-*a*]pyrazine were achieved by HPLC using a Chiralcel OD column (99MIP6). Separation of enantiomers of racemic 8-chloro-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline were achieved by HPLC using a Chiralcel OJ column and 10% *i*-PrOH in hexane containing 0.5%  $\text{Et}_2\text{NH}$  (96USP5576319).

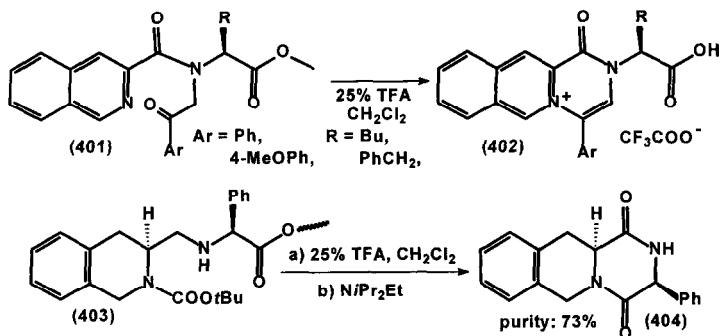
## C. SYNTHESIS

### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6+0( $\alpha$ )]

Treatment of the appropriate pipercolic amide **396** with  $\text{NEt}_3$  afforded optically active or racemic perhydropyrido[1,2-*a*]pyrazine-1,4-dione (**397**) (97USP5703072). (9*aS*)-Perhydropyrido[1,2-*a*]pyrazin-3-one (**400**) was obtained by cyclization of piperidine **398**, and the catalytic hydrogenation of quaternary salt **399** over Pd/C (99H(51)2065).

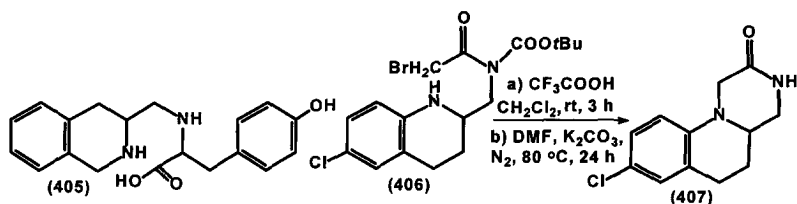


2-Substituted 4-aryl-1-oxo-1,2-dihydropyrazino[1,2-*b*]isoquinolinium salts **402** were obtained when 3-substituted isoquinolines **401** were cleaved from a polymer by treatment 25% TFA (00MIP5). *cis*-3,11*a*-H-3-Phenyl-1,2,3,4,11,11*a*-hexahydropyrazino[1,2-*b*]isoquinoline-1,4-dione (**404**) formed when isoquinoline derivative **403** was cleaved from a resin with 25% TFA during an automated solid-phase synthesis (98BMCL2369).



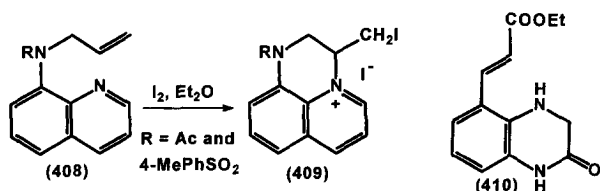
Cyclization of 1-(9-fluorenylmethoxycarbonyl)-2-[(*N*-methoxycarbonylmethyl)aminocarbonyl]piperidine and 2-(9-fluorenylmethoxycarbonyl)-3-[(*N*-methoxycarbonylmethyl)aminocarbonyl]-1,2,3,4-tetrahydroisoquinolines on the action of piperidine in THF yielded 2-(1,4-dioxoperhydropyrazido[1,2-*a*]pyrazin-2-yl)- and 2-(1,4-dioxo-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl)acetamides, respectively (99MIP11).

3-[(4-Hydroxyphenyl)methyl]-1,2,3,4,11,11*a*-hexahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-one (**347**,  $R = H$ ) was obtained by cyclization of 1,2,3,4-tetrahydroisoquinoline derivative **405** in acetone in the presence of TFA at ambient temperature overnight (97MI2). Ethyl ( $\alpha$ S,3*S*,11*a*S)-3-Methyl- $\alpha$ -(2-phenylethyl)-1,4-dioxo-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-2-acetate was identified in amorphous quinapril HCl as a degradation product (00JPS128, 00MI52).



8-Chloro-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinolin-2-one (**407**) was prepared when 6-chloro-2-[N-(2-bromoacetyl)-N-(tert-butoxycarbonyl)aminomethyl]-1,2,3,4-tetrahydroquinoline (**406**) was first treated with TFA, then the evaporated reaction mixture was heated in DMF in the presence of powdered  $K_2CO_3$  (96USP5576319).

Halocyclization of 8-(allylamino)quinolines **408** with  $I_2$  afforded 3-iodomethyl-2,3-dihydro-1H-pyrido[1,2,3-de]quinoxalium iodides **409** in good yields (97CHE680).



1,2,3,5,6,7-Hexahydropyrido[1,2,3-de]quinoxaline-2,5-dione (**387**) was obtained by catalytic hydrogenation of ethyl 3-(2-oxo-1,2,3,4-tetrahydro-5-quinoxaliny)acrylate (**410**) in a 1:1 mixture of MeOH and EtOH in the presence of *p*TSA over 5% Pd/C catalyst under 40 psi of hydrogen at ambient temperature for 40 h (96JMC4654).

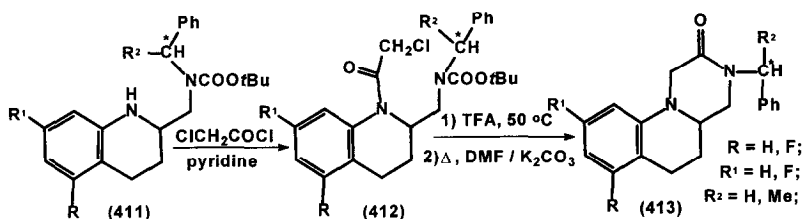
## 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [ $6+0(\beta)$ ]

Praziquantel (**9**) was prepared by the cyclization of 4-cyclohexylcarbonyl-1-phenethyl-2-oxo-1,2,3,4-tetrahydropyrazine in conc.  $H_2SO_4$  at room temperature in quantitative yield (98H(48)2279).

## 3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [ $6+0(\gamma)$ ]

Cyclization of (2*S*)-2-(*tert*-butoxycarbonylaminomethyl)-1-(2-chloroacetyl)piperidine on the action of NaH in THF gave (9*aS*)-2-(*tert*-butoxycarbonyl)perhydropyrido[1,2-*a*]pyrazin-4-one (99H(51)2065). 3-Benzyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-*a*]quinolin-1-ones **413**

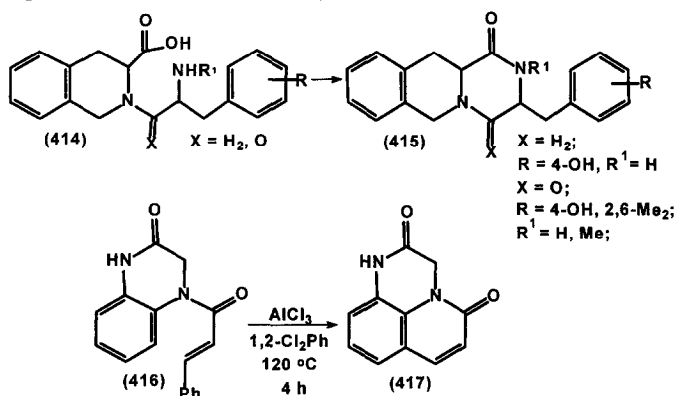
were obtained when 2-[*N*-benzyl-*N*-(*tert*-butoxycarbonyl)aminomethylene]-1-(2-chloroacetyl)-1,2,3,4-tetrahydroquinolines **412**, prepared from 1,2,3,4-tetrahydroquinolines **411** with  $\text{ClCH}_2\text{COCl}$ , was treated with TFA at  $50^\circ\text{C}$ , then the reaction mixture was heated in DMF in the presence of  $\text{K}_2\text{CO}_3$  (00MIP6, 01USP6169086).



8-Substituted perhydropyrido[1,2-*a*]pyrazine-1,4-diones were obtained when methyl *N*-[2-(benzyloxycarbonylamino)acetyl]-4-substituted pipercolinates were hydrogenated over 10% Pd/C catalyst in MeOH, and then the methanolic solutions were refluxed (00JAP(K)00/86659).

2-(2-Methoxy-5-nitrophenyl)perhydropyrido[1,2-*a*]pyrazin-3-one was obtained by cyclization of 1-(ethoxycarbonylmethyl)-2-[*N*-(2-methoxy-5-nitrophenyl)aminomethyl]piperidine on the action of NaH in boiling dioxane (99MIP10).

Diketopiperazine derivatives **415** ( $\text{X} = \text{O}$ ) and 2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinolin-1-one **415** ( $\text{X} = \text{H}_2$ ,  $\text{R} = 4\text{-OH}$ ,  $\text{R}' = \text{H}$ ) were prepared by cyclization of the corresponding 2-substituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **414** ( $\text{X} = \text{O}$ ,  $\text{H}_2$ ) in acetone at room temperature (97MI2, 97MI12).



Cyclization of 4-cinnamoyl-1,2,3,4-tetrahydroquinoxalin-2-one (**416**) by treatment with  $\text{AlCl}_3$  yielded 1,2,3,5-tetrahydropyrido[1,2,3-*de*]quinoxaline-2,5-dione (**417**) (96JMC4654).

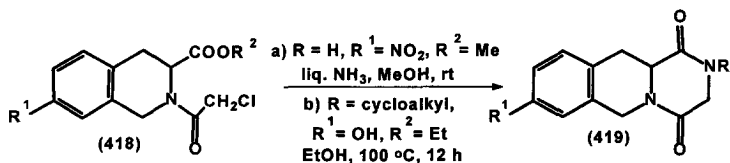
Cyclization of (2*R*,4*R*)-1-[[2-(3-methyl-1,2,3,4-tetrahydro-8-quinolylsulfonylamino)-2-[*N*<sup>3</sup>-(4-methoxy-2,3,6-trimethylbenzenesulfonyl)guanidinopropyl]acetyl}-4-methyl-pipecolic acid on the action of *N*-hydroxybenzotriazole and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in the presence of *i*-Pr<sub>2</sub>N<sup>+</sup>Et in CH<sub>2</sub>Cl<sub>2</sub> at room temperature gave (3*S*,8*R*,9*aR*)-2-(3-methyl-1,2,3,4-tetrahydro-8-quinolylsulfonyl)-3-[3-(*N*<sup>3</sup>-4-methoxy-2,3,6-trimethylbenzenesulfonyl)guanidinopropyl]perhydropyrido[1,2-*a*]pyrazine-1,4-dione (01MIP18). Treatment of optically active allyl 1-[2-(9-fluorenylmethoxycarbonyloxyamino)-2-substituted acetyl]pipecolinate with piperidine in CH<sub>2</sub>Cl<sub>2</sub> at room temperature yielded optically active 3-substituted perhydropyrido[1,2-*a*]pyrazine-1,4-diones (01MIP18).

Perhydropyrido[1,2-*a*]pyrazine-1,6-diones and 6*a*,7,8,9-tetrahydro-5*H*-pyrido[1,2-*a*]quinoxaline-6,10-diones were formed when their precursors bond to a resin were cleaved by an acid (01MIP4).

Catalytic hydrogenation of 2-cyano-1-(2-nitrophenyl)piperidines over Pearlman's catalyst in a low-pressure hydrogenator under 1 atm of hydrogen in dioxane gave cyclic amidine *N*-oxides **352** (01EJOC987).

#### 4. By Formation of Two Bonds from [5+1] Atom Fragments

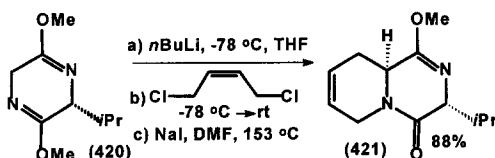
Cyclocondensation of 2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **418** (R<sup>1</sup>=NO<sub>2</sub>, R<sup>2</sup>=Me) with liquid NH<sub>3</sub> in MeOH in a stainless steel pressure vessel at room temperature overnight gave 8-nitro-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**419**, R=H, R<sup>1</sup>=NO<sub>2</sub>) (97MIP4). (11*aR*)-2-Cycloalkyl-8-hydroxy-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones **419** (R=cycloalkyl, R<sup>1</sup>=OH) were prepared in the reactions of (3*R*)-2-chloroacetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**418**, R<sup>1</sup>=OH, R<sup>2</sup>=Et) with cycloalkylamines (98MIP7).



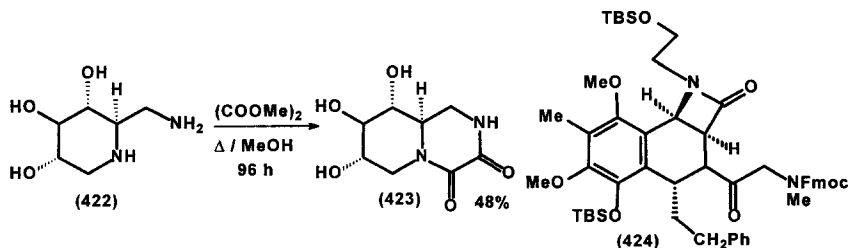
Reaction of ethyl 7-bromo-8-fluoro-1-(2-bromo-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate with MeNH<sub>2</sub> yielded 10-bromo-*N*,1,3-trimethyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]quinoxaline-3-carboxamide (00MIP10).

## 5. By Formation of Two Bonds from [4+2] Atom Fragments

Treatment of bis-lactim ether **420** with BuLi, then with *cis*-1,4-dichloro-2-butene in the presence of NaI afforded 3,4,9,9a-tetrahydro-6*H*-pyrido[1,2-*a*]pyrazin-4-one (**421**) with 96% diastereomeric excess (97TA1855). Reaction of 1,2-diphenyl-6-methyl-quinoxaline with 1,4-dichlorobutane in THF in the presence of Na at  $-78^{\circ}\text{C}$  afforded a 3:1 mixture of 4*a*,5-diphenyl-9-methyl-1,2,3,4-tetrahydro-4*aH*-pyrido[1,2-*a*]quinoxaline and 4-(4-chlorobutyl)-2,3-diphenyl-6-methyl-1,4-dihydroquinoxaline (98JHC1349).



Cyclocondensation of 2-aminomethylpiperidine **422** and dimethyl oxalate yielded perhydropyrido[1,2-*a*]pyrazine-3,4-dione **423** (00T1005).



## 6. By Formation of Two Bonds from [3+3] Atom Fragments

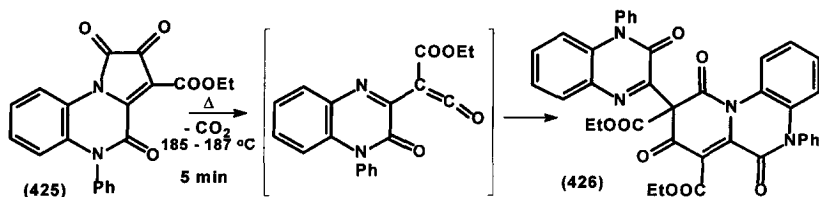
Cyclocondensation of 1-methyl-1,2,3,4-tetrahydroquinoxalines and triethyl methanetricarboxylate at  $150^{\circ}\text{C}$  for 2 h, then at  $200^{\circ}\text{C}$  for 6 h gave 7-hydroxy-1-methyl-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]quinoxalines (00MIP10).

## 7. Ring Transformation

1,3,4,6,11,11*a*-Hexahydro-2*H*-pyrazino[2,1-*b*]isoquinoline-1,4-dione **351** was obtained by the treatment of tricyclic derivative **424** with piperidine (01TL543).

Thermolysis of tricyclic **425** in Dowtherm A afforded 6,8,10-trioxo-9,10-dihydro-6*H*-pyrido[1,2-*a*]quinoxaline-7,9-dicarboxylate **426** (00CHE615).

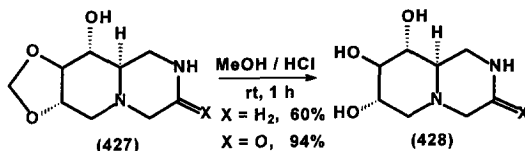




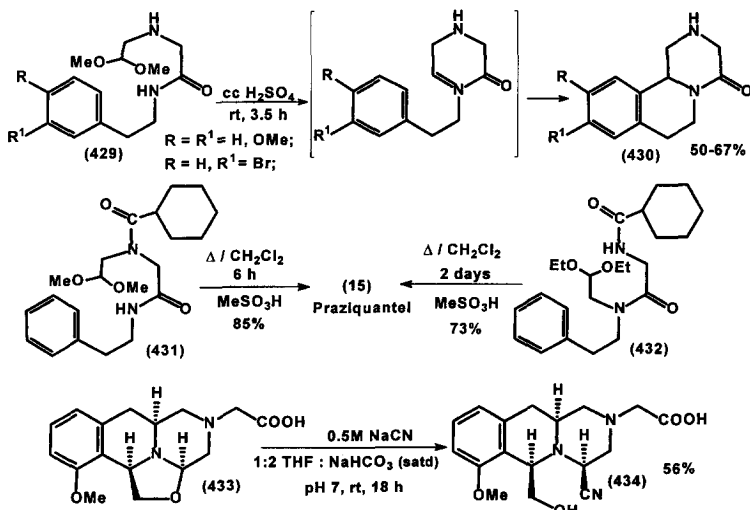
Reaction of  $\text{NH}_4\text{OAc}$  and 2-(4-nitrophenyl)pyrido[1,2,3-*de*]-1,4-benzoxazinium bromide (**296**,  $\text{X}=\text{O}$ ,  $\text{R}=\text{NO}_2$ ) in boiling  $\text{AcOH}$  gave 2-(4-nitrophenyl)-1*H*-pyrido[1,2,3-*de*]quinoxalinium bromide (**296**,  $\text{X}=\text{NH}$ ,  $\text{R}=\text{NO}_2$ ) (98MI45).

### 8. Miscellaneous

Treatment of tricyclic nitrogen bridgehead compounds **427** with acidified  $\text{MeOH}$  gave 7,8,9-trihydroxyperhydropyrido[1,2-*a*]pyrazines **428** (00T1005).

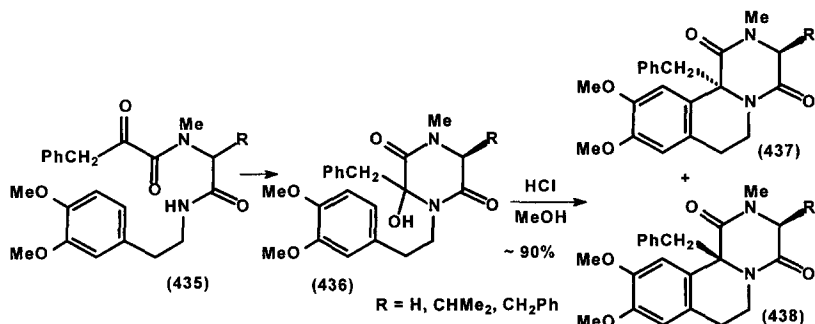


1,2,3,5,6,11*a*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones **430** and praziquantel (**9**) were obtained from acetals **429**, **431** and **432** on the action of conc.  $\text{H}_2\text{SO}_4$  at room temperature (98T7395) and  $\text{MeSO}_3\text{H}$  in a boiling solvent (98H(48)2279), respectively.



Treatment of tetracyclic nitrogen bridgehead compound **433** with NaCN resulted the formation of 4-cyano derivative of 1,2,3,4,11a-hexahydro-6*H*-pyrazino[1,2-*b*]isoquinoline **434** (00BMC523).

Treatment of compound **435** (R = H) and piperazine-2,5-dione **436** (R = *i*-Pr) with methanolic HCl gave pyrazino[2,1-*a*]isoquinoline-1,4-diones **437** (R = H, *i*-Pr). Benzyl derivative **436** (R = PhCH<sub>2</sub>) afforded a 9 : 1 mixture of **437** and **438** (R = CH<sub>2</sub>Ph) (01OL997).



Racemic *trans*-2-(1-naphthylsulfonyl)-7-{{4-amino-2-quinaxolynyl}amino-methyl}perhydropyrido[1,2-*a*]pyrazine was resolved into the optically active enantiomers by means of a Chiralpack column (01MIP20).

## D. APPLICATIONS AND IMPORTANT COMPOUNDS

Discovery of potent and selective dopamine D<sub>4</sub> receptor antagonists, 2-(2-pyrimidyl)-7-(phenoxy)methylperhydropyrido[1,2-*a*]pyrazines, was summarized (98MI73). (7*R*,9*aS*)-7-[4-Fluorophenoxy)methyl]-2-(5-fluoro-2-pyrimidyl)perhydropyrido[1,2-*a*]pyrazine HCl (CP-293,019), a selective D<sub>4</sub> antagonist, may be effective in the treatment of schizophrenia (98MI34), and its regiospecific induction of ΔFosβ was investigated (99MI38). Its effects was compared with those of the generic D<sub>2</sub>-like antagonist haloperidol to identify any characteristic “ethogram” in terms of individual topologies of behavior within the natural rodent repertoire (00MI47).

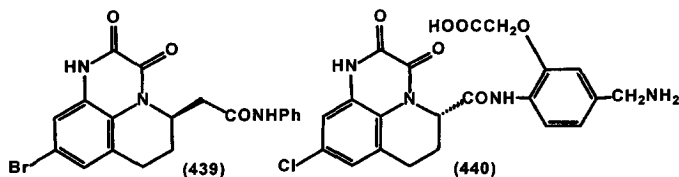
Synthesis, pharmacology, pharmacokinetics and metabolism of **4** was reviewed (98MI28). Sunepitron (**4**) is undergoing clinical phase II trials for the indications of generalized anxiety disorder and major depressive disorder. Metabolism and excretion of **4** were studied (97MI58, 97MI59, 98MI67). Combination of **4** with other drug was patented (00MIP16).

4-(3,4-Dichlorophenyl)-2-[2-(perhydropyrido[1,2-*a*]pyrazin-2-yl)benzylidene]thiomorpholin-3-one was claimed as a psychotherapeutic agent (98MIP6). Inhibitory concentration and proportion of high and low affinity

binding sites of 2-[(3,4,5-trimethoxyphenyl)methyl]perhydropyrido[1,2-*a*]pyrazine for [ $^3\text{H}$ ]-trimetazidine binding sites in rat liver mitochondria were determined (00BJP655).

Inhibition of human multidrug resistance P-glycoprotein 1 was investigated by analogs of a potent  $\delta$ -opioid antagonist, including (3*S*,11*aS*)-3-[(4-hydroxy-2,6-dimethylphenyl)methyl]-11,11*a*-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (01MI10). Opioid antagonist activity of 3-arylmethyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones were studied (97MI2, 97MI12, 97MI21). (11*aR*)-2-Cyclopentyl-7-(2-propenyl)-8-[(4-cyanophenyl)methoxy]- and 8-(2-pyridylmethoxy)-11,11*a*-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones were patented as apolipoprotein 3-secretion/microsomal triglyceride transfer protein inhibitors (01EUP1099442). Manufacture of antitumor 2-acetyl-1,2,11,11*a*-tetrahydro- and 2-acetyl-1,2,3,4,11,11*a*-hexahydro-3-benzoyl- and -3-benzyl-10-(7-methoxy-1,3-benzodioxol-5-yl)-6*H*-pyrazino[1,2-*b*]isoquinolin-6-ones by culturing *Chrysosporium* was patented (01JAP(K)01/139577). (11*aR*)-2-Cyclopentyl-7-(propenyl)-8-(2-pyridylmethoxy)-11,11*a*-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-diones was patented as microsomal triglyceride transfer protein inhibitor (00JAP(K)00/169395).

Syntheses of praziquantel (**9**) were reviewed (99MI2). The acute and subacute toxicities of liposome-bound **9** were studied (98MI105). Efficacy of **9** was investigated *in vitro* and *in vivo* (98MI103, 98MI104, 99MI44, 99MI46, 99MI47, 99MI48, 00MIP8). 1-Praziquantel proved to be the active enantiomer when enantiomers of **9** were tested for activity against juvenile *Schistosoma mansoni* infestations in mice (99MI51). Resistance to **9** was reported (99MI50), and reviewed (97MI64). Pharmacoeconomy of the treatment of schistosomiasis with **9** was reviewed (00MI53). Chemotherapy of schistosomiasis was reviewed and **9** is the drug of choice (98MI61, 99AF557). Praziquantel was patented as a component in fungicides, bactericides, and herbicides (00GEP19854402). Different formulations and combinations of **9** with other anthelmintics were developed and patented (96GEP19520275, P19601263, P19628776, 96MI5, 96MI22, 97MI23, 97MIP6, P14, 98MI29, 98MI41, 98MIP3, P4, P8, P10, P20, 99CPB1629, 99JAP(K)99/60485, P(K)99/92309, 99MI45, 99MIP5, 00MIP8, 01MIP11, P15). Levo- and racemic **9** were encapsulated in liposomes (99MI53).



Among others 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxalines **439** and **440** were investigated as glycine/NMDA receptor antagonists (97JMC4053, 97MIP11, 98MI17, 98MI44).

## REFERENCES

- 61HC(15-2)1180 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1180 (1961).  
 61HC(15-2)1182 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1182 (1961).  
 61HC(15-2)1188 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1188 (1961).  
 61HC(15-2)1191 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1191 (1961).  
 61HC(15-2)1192 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1192 (1961).  
 61HC(15-2)1193 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1193 (1961).  
 61HC(15-2)1201 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1201 (1961).  
 61HC(15-2)1203 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1203 (1961).  
 61HC(15-2)1207 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1207 (1961).  
 61HC(15-2)1211 W. L. Mosby, *Chem. Heterocycl. Compd.* **15-2**, 1211 (1961).  
 67JMC223 H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Med. Chem.* **10**, 223 (1967).  
 68USP3408347 J. Shavel, Jr. and H. Zinnes, U.S. Pat. 3,408,347 (1968) [CA **70**, 68,387 (1969)].  
 77TL631 J. J. Köhler and W. N. Speckamp, *Tetrahedron Lett.*, 631 (1977).  
 78JCS(CC)166 W. N. Speckamp and J. J. Köhler, *J. Chem. Soc., Chem. Commun.*, 166 (1978).  
 80JCS(CC)142 H. J. Köhler and W. N. Speckamp, *J. Chem. Soc., Chem. Commun.*, 142 (1980).  
 81CSC121 A. M. F. Brouwers and C. H. Stam, *Cryst. Struct. Commun.* **10**, 121 (1981).  
 86AHC(39)281 I. Hermecz and L. Vasvári-Debreczy, *Adv. Heterocycl. Chem.* **39**, 281 (1986).  
 94MI1 N. I. Makarova, V. A. Kharlanov, and M. I. Knyazhanskii, *Khimiya* 106 (1994) [CA **125**, 57,671 (1996)].  
 94TL595 M. Naruse, S. Aoyagi, and C. Kibayashi, *Tetrahedron Lett.* **35**, 595 (1994).  
 95MI1 M. Y. Ebeid, H. H. Hassanein, and N. Obidan, *Bull. Fac. Pharm. (Cairo Univ.)* **33**, 41 (1995) [CA **125**, 33,946 (1996)].  
 95MI2 G. Fardella, P. Barbetti, I. Chiappini, V. Ambrogio, and G. Grandolini, *Acta Technol. Legis Med.* **6**, 269 (1995).  
 96BCJ1371 D. Barrett, H. Sasaki, T. Kinoshita, H. Tsutsumi, and K. Sakane, *Bull. Chem. Soc. Jpn.* **69**, 1371 (1996).  
 96CHCII(8)563 I. Hermecz, L. Vasvári-Debreczy, and P. Mátyus, *Compr. Heterocycl. Chem. II* **8**, 563 (1996).  
 96CJC2434 S. Mill and C. Hootelé, *Can. J. Chem.* **74**, 2434 (1996).  
 96CP2176298 D. D. Copeland, K. M. Ewert, and T. S. Wollen, Can. Pat. 2,176,298 (1996) [CA **126**, 255,500 (1997)].  
 96GEP19520275 N. Mencke, A. Harder, P. Jeschke, and B. Helpap, Ger. Pat. 19,520,275 (1996) [CA **126**, 84,585 (1997)].  
 96GEP19601263 J. Kalbe and H. Schnabel, Ger. Pat. 19,601,263 (1996) [CA **127**, 140,562 (1997)].

- 96GEP19628776 J. Kalbe and T. Hopkins, Ger. Pat. 19,628,776 (1996) [CA 128, 119,688 (1998)].
- 96JAP(K)96/291144 S. Ono, T. Santo, H. Yamamoto, T. Takakura, H. Kotsubo, Y. Furuta, and H. Kaga, Jpn. Kokai 96/291,144 (1996) [CA 126, 74,860 (1997)].
- 96JCS(P1)1113 M. Naruse, S. Aoyagi, and C. Kibayashi, *J. Chem. Soc., Perkin Trans. I*, 1113 (1996).
- 96JCS(P1)2077 M. Naruse, S. Aoyagi, and C. Kibayashi, *J. Chem. Soc., Perkin Trans. I*, 2077 (1996).
- 96JMC4654 J. W. Mickelson, E. J. Jacobsen, D. B. Carter, H. K. Im, W. B. Im, J. K. D. Peggy, V. H. Sethy, A. H. Tang, J. E. McGee, J. D. Petke, *J. Med. Chem.* **39**, 4654 (1996).
- 96JOC4423 A. Kotschy, Gy. Hajós, G. Timári, and A. Messmer, *J. Org. Chem.* **61**, 4423 (1996).
- 96MI1 E. N. Padeiskaya, *Antibiol. Khimioter.* **41**, 13 (1996) [CA 126, 303,471 (1997)].
- 96MI2 D. G. Kim and E. R. Sakirova, *Izv. Vyssh. Ucheb., Zaved., Khim. Khim. Technol.* **39**, 15 (1996) [CA 126, 185,967 (1997)].
- 96MI3 V. P. Yakovlev, *Antibiol. Khimioter.* **41**, 24 (1996) [CA 126, 311,598 (1997)].
- 96MI4 E. J. C. Goldstein, *Clin. Infect. Dis.* **23**(Suppl.), S25 (1996).
- 96MI5 F. S. Mikhailitsyn, N. L. Sergovskaya, M. N. Lebedeva, B. A. Astafer, G. A. Gitsy, D. G. Bayandina, N. A. Uvarova, and N. D. Lychko, *Med. Parazitol. Bolezni* **36** (1996) [CA 127, 199,644 (1997)].
- 96MI6 Y. Chen, F. Han, and Z. Yuan, *Fenxi Ceshi Xuebao* **15**, 63 (1996) [CA 126, 109,004 (1996)].
- 96MI7 G. Condorelli, G. De Guidi, S. Ginfrida, P. Miano, S. Sortino, and A. Velardita, *Med. Biol. Environ.* **24**, 103 (1996).
- 96MI8 Y. Hu, Y. Xia, D. Zhou, L. Xiang, L. Huang, W. Le, and J. Mei, *Huaxi Yaoxue Zazhi* **11**, 129 (1996) [CA 126, 18,842 (1997)].
- 96MI9 M. B. Delgado and A. Telenti, *PCR Protoc. Emerging Infect. Dis.* **138** (1996) [CA 126, 1764 (1997)].
- 96MI10 K.-S. Nam and Y.-W. Park, *Korean J. Med. Chem.* **6**, 157 (1996) [CA 126, 131,367 (1997)].
- 96MI11 C. J. Veiopoudou, E. S. Lianidou, P. C. Ionnou, and C. E. Efstathiou, *Anal. Chim. Acta* **335**, 177 (1996).
- 96MI12 K.-S. Nam, B.-J. Kim, T.-S. Lee, and W.-J. Kim, *Korean J. Med. Chem.* **6**, 203 (1996) [CA 126, 157,377 (1997)].
- 96MI13 M. Warowna-Grzeskiewicz, J. Chodkowski, and Z. Fijalek, *Acta Pol. Pharm.* **53**, 241 (1996).
- 96MI14 Q. Zhang and J. Gao, *Zhongguo Yaowu Huaxue Zazhi* **6**, 262 (1996) [CA 127, 205,370 (1997)].
- 96MI15 R. Cruz, N. Lopez, M. Quintero, and G. Rojas, *J. Math. Chem.* **20**, 385 (1996) (Pub. 1997).
- 96MI16 E. Wang, X. Zhang, B. Wu, and S. Dong, *Zhongguo Yaoke Daxue Xuebao* **27**, 449 (1996) [CA 126, 162,100 (1997)].
- 96MI17 X. Zhang and X. Yao, *Zhongguo Yaoke Daxue Xuebao* **27**, 480 (1996) [CA 126, 148,586 (1997)].
- 96MI18 J. Wang and Z. Huang, *Zhongguo Yiyao Gongye Zazhi* **27**, 512 (1996) [CA 127, 39,958 (1997)].

- 96MI19 J. Tan and F. Cao, *Zhongguo Yaoke Daxue Xuebao* **27**, 518 (1996) [*CA* **126**, 245,937 (1997)].
- 96MI20 H. Zhou, Y. Guo, L. Sheng, B. Xiang, and D. An, *Zongguo Yaoke Daxue Xuebao* **27**, 547 (1996) [*CA* **126**, 185,737 (1997)].
- 96MI21 G. C. Schito, J. F. Acar, A. Bauernfeld, J. Dural, R. G. Finch, J. Focht, G. Nicoletti, I. Phillips, and G. Pratts, *J. Antimicrob. Chemother.* **38**, 627 (1996).
- 96MI22 J. Song, J. Liang, N. Xu, and L. Zhou, *Zhongguo Yaoke Daxue Xuebao* **27**, 665 (1996) [*CA* **127**, 39,652 (1997)].
- 96MI23 Z. Zhang, X. He, Y. Li, and S. Qu, *Yaoxue Xuebao* **31**, 695 (1996) [*CA* **126**, 203,806 (1997)].
- 96MI24 D. D'Antonio, E. Pizzigallo, A. Iacone, B. Violante, A. Di Marzio, M. Lombardo, G. Fioritoni, T. Staniscia, and F. Romano, *J. Antimicrob. Chemother.* **38**, 839 (1996).
- 96MI25 I. Mahmood and J. O. Balian, *Xenobiotica* **26**, 887 (1996).
- 96MIP1 J. F. Hartmann and D. Farcasin, *PCT Int. Appl.* 96/40,156 (1996) [*CA* **126**, 144,048 (1997)].
- 96MIP2 D. Farcasiu, J. F. Hartmann, P. Herczeg, and F. Sztaricskai, *PCT Int. Appl.* 96/40190 (1996) [*CA* **125**, 152,783 (1996)].
- 96TAL2123 V. Kapetanovic, Lj. Milovanovic, and M. Erceg, *Talanta* **43**, 2123 (1996).
- 96USP5576319 R. Baker, J. J. Kulagowski, N. R. Curtis, P. D. Leeson, M. P. Ridgill, and A. L. Smith, U.S. Pat. 5,576,319 (1996) [*CA* **126**, 59,972 (1997)].
- 97AAC927 L. Aguilar, M. J. Gimenez, J. Costa, R. Dal-Re, and J. Prieto, *Antimicrob. Agents Chemother.* **41**, 927 (1997).
- 97AAC1256 H. Jung, R. Medina, N. Castro, T. Corona, and J. Sotelo, *Antimicrob. Agents Chemother.* **41**, 1256 (1997).
- 97AAC2196 L.-J. Lee, B. Hafkin, I.-D. Lee, J. Hoh, and R. Dix, *Antimicrob. Agents Chemother.* **41**, 2196 (1997).
- 97ACS896 V. Sanz-Nebot, I. Walls, D. Barbero, and J. Barbosa, *Acta Chem. Scand.* **51**, 896 (1997).
- 97AJC109 A. M. W. Cargill Thompson, S. R. Batten, J. C. Jeffery, L. H. Rees, and M. D. Ward, *Aust. J. Chem.* **50**, 109 (1997).
- 97ANC4143 D. A. Volmer, B. Mansoori, and S. J. Locke, *Anal. Chem.* **69**, 4143 (1997).
- 97BJP743 J. E. Souness, C. Hoghton, N. Sardar, and M. T. Withnall, *Br. J. Pharmacol.* **121**, 743 (1997).
- 97BJP759 S. Ballaz, A. Barber, A. Fortuño, J. Del Río, M. Martín-Martínez, I. Gómez-Monterrey, R. Herranz, R. González-Muñiz, and M.-T. García-López, *Br. J. Pharmacol.* **121**, 759 (1997).
- 97CEJ1588 K. Beck, P. Hoffman, and S. Hünig, *Chem. Eur. J.* **3**, 1588 (1997).
- 97CHE96 V. Mitskyavichyus, *Chem. Heterocycl. Compd. (N. Y.)* **33**, 96 (1997).
- 97CHE680 D. V. Vorob'ev, Y. V. Tikhonova, D. G. Kim, and A. V. Belik, *Chem. Heterocycl. Compd. (N. Y.)* **33**, 680 (1997).
- 97CHE989 D. G. Kim, *Chem. Heterocycl. Compd. (N. Y.)* **33**, 989 (1997).
- 97CP2188071 R. C. S. H. Leung-Toung, K. Karimian, and T. F. Tam, *Can. Pat.* 2,188,071 (1997) [*CA* **127**, 190,648 (1997)].
- 97EUP768302 P. Zbinden, *Eur. Pat.* 768,302 (1997) [*CA* **126**, 343,499 (1997)].
- 97H(45)137 S. B. Kang, S. Park, Y. H. Kim, and Y. Kim, *Heterocycles* **45**, 137 (1997).

- 97HCA1161 C.-C. Tzeng, Y.-L. Chen, C.-J. Wang, T.-C. Wang, Y.-L. Chang, and C.-M. Teng, *Helv. Chim. Acta* **80**, 1161 (1997).
- 97IJC(B)349 B. Lai and R. M. Gidwani, *Indian J. Chem. B* **36B**, 349 (1997).
- 97JA962 A. B. Smith, III, S. M. Condon, J. A. McCauley, J. L. Leazar, Jr., J. W. Leahy, and R. E. Maleczka, Jr., *J. Am. Chem. Soc.* **119**, 962 (1997).
- 97JA6446 T. M. Zabriskie, W. L. Kelly, and X. Liang, *J. Am. Chem. Soc.* **119**, 6446 (1997).
- 97JAP(K)97/59303 J. Kyota and N. Ueno, *Jpn. Kokai* 97/59,303 (1997) [*CA* **126**, 279,255 (1997)].
- 97JAP(K)97/124486 K. Itokazu, *Jpn. Kokai* 97/12486 (1997) [*CA* **127**, 55,921 (1997)].
- 97JAP(K)97/236581 T. Arai and T. Horigome, *Jpn. Kokai* 97/236,581 (1997) [*CA* **127**, 305,035 (1997)].
- 97JC(A)215 S.-W. Sun and L.-Y. Chen, *J. Chromatogr. A* **766**, 215 (1997).
- 97JC(A)233 S. T. Colgan, R. H. Reed, M. L. Dumont, and G. R. Haggan, *J. Chromatogr. A* **764**, 233 (1997).
- 97JC(A)235 T. Horimai, M. Ohara, and M. Ichinose, *J. Chromatogr. A* **760**, 235 (1997).
- 97JC(B)141 J. Liu and J. T. Stewart, *J. Chromatogr. B* **692**, 141 (1997).
- 97JC(B)147 H.-J. Kraemer, R. Gehrke, A. Breithaupt, and H. Breithaupt, *J. Chromatogr. B* **700**, 147 (1997).
- 97JC(B)307 V. A. P. Jabor, G. M. Rocha, and P. S. Bonato, *J. Chromatogr. B* **696**, 307 (1997).
- 97JCS(P1)2163 S. Brocherieux-Lanoy, H. Dhimane, J.-C. Poupon, C. Vanucci, and G. Lhomme, *J. Chem. Soc., Perkin Trans. 1*, 2163 (1997).
- 97JCS(P1)3591 T. Uetake, M. Nishikawa, and M. Tada, *J. Chem. Soc., Perkin Trans. 1*, 3591 (1997).
- 97JHC1813 G. E. Boswell, D. L. Musso, A. D. Davis, J. L. Kelley, F. E. Soroko, and B. R. Cooper, *J. Heterocycl. Chem.* **34**, 1813 (1997).
- 97JMC3402 M. Martín-Martínez, J. M. Bartolomé-Nebreda, I. Gómez-Monterrey, R. González-Muñiz, M. T. García-López, S. Ballaz, A. Barber, A. Fortuño, J. Del Río, R. Herranz, *J. Med. Chem.* **40**, 3402 (1997).
- 97JMC4053 M. Rewley, J. J. Kulagowski, A. P. Watt, D. Rathbone, G. I. Stevenson, R. W. Carling, R. Baker, G. R. Marshall, J. A. Kemp, A. C. Foster, S. Grimwood, R. Hargreaves, C. Hurley, K. L. Saywell, M. D. Tricklebank, P. D. Leeson, *J. Med. Chem.* **40**, 4053 (1997).
- 97JOC2080 M. I. Collado, I. Manteca, N. Sotomayor, M.-J. Villa, and E. Lete, *J. Org. Chem.* **62**, 2080 (1997).
- 97LA1165 F. Fülöp, J. Tari, G. Bernáth, P. Sohár, A. Dancsó, Gy. Argay, and A. Kálmán, *Liebigs Ann./Recl.*, 1165 (1997).
- 97MI1 E. Wang, X. Zhu, and R. Liu, *Zhongguo Yaoke Daxue Xuebao* **28**, 5 (1997) [*CA* **127**, 346,356 (1997)].
- 97MI2 G. Balboni, R. Guerrini, S. Salvadori, R. Tomatis, S. D. Bryant, C. Bianchi, M. Attila, and L. H. Lazarus, *Biol. Chem.* **378**, 19 (1997).
- 97MI3 E. Mateos, S. Piriz, J. Valle, M. Hurtado, and S. Vadillo, *J. Vet. Pharmacol. Ther.* **20**, 21 (1997).
- 97MI4 Y. Mao, X. Luo, and Y. Rao, *Zhongguo Yiyuan Yaoxue Zazhi* **17**, 23 (1997) [*CA* **127**, 210,270 (1997)].

- 97MI5 N. Rivero, B. Llorente, and R. Carrasco, *Rev. CENIC Cienc. Quim.* **28**, 25 (1997) [CA **127**, 242,828 (1997)].
- 97MI6 E. N. Padeiskaya, *Antibiot. Khimioter.* **42**, 26 (1997) [CA **128**, 225,432 (1998)].
- 97MI7 G. A. Saleh, *Bull. Pharm. Sci., Assiut Univ.* **20**, 27 (1997) [CA **127**, 351,330 (1997)].
- 97MI8 B. P. Imbimbo, W. Kletmann, G. P. Broccali, M. Cesana, and L. Aarons, *Eur. J. Pharm. Sci.* **5**, 37 (1997).
- 97MI9 Y. Hu, D. Zhou, L. Xiang, W. Le, and Y. Mei, *Zhongguo Yaowu Huaxue Zazhi* **7**, 37 (1997) [CA **127**, 214,639 (1997)].
- 97MI10 B. Lin, X. Zhu, B. Koppenhoefer, and U. Epperlein, *LC-GC* **15**, 40 (1997).
- 97MI11 Y.-J. Chung, S.-K. Kim, and E.-C. Choi, *J. Gen. Appl. Microbiol.* **43**, 61 (1997).
- 97MI12 O. Crescenzi, F. Fraternali, D. Picone, T. Tancredi, G. Balboni, R. Guerrini, L. H. Lazarus, S. Savadori, and P. A. Temussi, *Eur. J. Biochem.* **247**, 66 (1997).
- 97MI13 S. Ozyazgan, V. Sensen, Z. Ozuner, and A. G. Akkan, *J. Basic Clin. Physiol. Pharmacol.* **8**, 73 (1997).
- 97MI14 H. F. Askal, *Bull. Pharm. Sci., Assiut Univ.* **20**, 75 (1997) [CA **127**, 351,331 (1997)].
- 97MI15 C. Rao, Y. Sun, J.-C. Liu, and J. Wang, *Drug Delivery* **4**, 81 (1997).
- 97MI16 A. M. Bergold and C. Salvatoretti, *Rev. Farm. Bioquim. Univ. Sao Paulo* **33**, 85 (1997) [CA **129**, 58,894 (1998)].
- 97MI17 I. L. Ivankiv, V. V. Djackok, and O. R. Sjarkevich, *Pharm. Zh. (Kiev)* **85** (1997) [CA **128**, 26,992 (1998)].
- 97MI18 H. Gu, L. Sun, X. Wu, Z. Tao, and S. Zhao, *Yaowu Fenxi Zazhi* **17**, 89 (1997) [CA **127**, 336,731 (1997)].
- 97MI19 K.-I. Yamaki, T. Hasegawa, I. Matsuda, M. Nadai, H. Aoki, and K. Takagi, *J. Infect. Chemother.* **3**, 97 (1997).
- 97MI20 D. N. Fish and A. T. Chow, *Clin. Pharmacokinet.* **32**, 101 (1997).
- 97MI21 S. D. Bryant, G. Balboni, R. Guerrini, S. Salvadori, R. Tomatis, and L. H. Lazarus, *Biol. Chem.* **378**, 107 (1997).
- 97MI22 A. Shan, Y. Lu, and J. Li, *Zhongguo Linchuang Yaolixue Zazhi* **13**, 115 (1997) [CA **128**, 196,501 (1998)].
- 97MI23 B. Lu, H. Zhong, and H. Yang, *Zhongguo Yiyao Gongye Zazhi* **28**, 159 (1997) [CA **127**, 336,577 (1997)].
- 97MI24 F. Li, H. Jin, J. Gu, R. Fu, and R. Dai, *Beijing Ligong Daxue Xuebao* **17**, 166 (1997) [CA **128**, 93,290 (1998)].
- 97MI25 P. Zhang, Q. Shi, B. Wu, and Q. Cheng, *Hangzhou Daxue Xuebao Ziran Kexueban* **24**, 166 (1997) [CA **128**, 93,287 (1998)].
- 97MI26 H. Gu, Z. Tao, S. Zhao, X. Wu, L. Chen, and Y. Jiang, *Zhongguo Yiyao Gongye Zazhi* **28**, 169 (1997) [CA **127**, 283,473 (1997)].
- 97MI27 S. Okonogi, T. Oguchi, E. Yonemochi, S. Puttipatkhachorn, and K. Yamamoto, *Int. J. Pharm.* **156**, 175 (1997).
- 97MI28 E. Kantharaj and V. S. Iyer, *Indian J. Heterocycl. Chem.* **6**, 177 (1997).
- 97MI29 S. Ma and M. Li, *Yaowu Fenxi Zazhi* **17**, 179 (1997) [CA **128**, 66,397 (1998)].



- 97MI30 R. J. Atkins, G. F. Breen, L. P. Crawford, T. J. Grinter, M. A. Harris, J. F. Hayes, C. J. Moores, R. N. Saunders, A. C. Share, T. C. Walsgrove, C. Wicks, *Org. Process Res. Dev.* **1**, 185 (1997).
- 97MI31 R. Soler Roca, J. Galvez Alvarez, R. Garcia-Domenech, M. T. Salabert Salvador, C. D. Gregoria Alapont, and M. D. Garcia Lopez, *An. R. Acad. Farm.* **63**, 191 (1997) [*CA* **127**, 171,093 (1997)].
- 97MI32 A. I. Drakopoulos and P. C. Ioannou, *Anal. Chim. Acta* **354**, 197 (1997).
- 97MI33 J. Yu, Y. Wang, and G. Luo, *Yaoxue Xuebao* **32**, 203 (1997) [*CA* **128**, 72,527 (1998)].
- 97MI34 J. Zhang, T. Zhang, Z. Hong, and C. Huang, *Shenyang Yaoke Daxue Xuebao* **14**, 216 (1997) [*CA* **129**, 221,233 (1998)].
- 97MI35 L. Sun, *Zhongguo Yiyao Gongye Zazhi* **28**, 261 (1997) [*CA* **127**, 283,466 (1997)].
- 97MI36 E. Memin, G. Panteix, and A. Revol, *J. Antimicrob. Chemother.* **40**, 263 (1997).
- 97MI37 J. Lei, R. Zhang, S. Luo, H. Cai, and Y. Xiang, *Yaowu Fenxi Zazhi* **17**, 295 (1997) [*CA* **129**, 65,052 (1998)].
- 97MI38 C.-K. Lai, T. Lee, K.-M. Au, and Y.-W. Albert, *Clin. Chem. (Washington DC)* **43**, 312 (1997).
- 97MI39 X. Zhang, W. Wen, J. Jiang, S. Luo, and H. Cai, *Zhongguo Yiyao Gongye Zazhi* **28**, 314 (1997) [*CA* **128**, 299,620 (1998)].
- 97MI40 K. Yoshida, K. Matsubayashi, M. Sekiguchi, and I. Hayakawa, *Chemotherapy (Basel)* **43**, 332 (1997).
- 97MI41 W. Xiong and E. Wang, *Yaoxue Xuebao* **32**, 347 (1997) [*CA* **127**, 358,825 (1997)].
- 97MI42 C. Yin and Y. Wu, *Yaowu Fenxi Zazhi* **17**, 371 (1997) [*CA* **129**, 140,762 (1998)].
- 97MI43 M. Tong, C. Dai, W. Zhao, P. Yang, and Y. Mei, *Zhongguo Kangshengsu Zazhi* **22**, 384 (1997) [*CA* **129**, 211,266 (1998)].
- 97MI44 J. Barbosa, I. Marques, G. Fonrodona, D. Barron, and R. Berges, *Anal. Chim. Acta* **347**, 385 (1997).
- 97MI45 S. Zhang, C. Wu, Z. Zhang, and H. Zhou, *Zhongguo Yiyuan Yaoxue Zazhi* **17**, 454 (1997) [*CA* **128**, 274,927 (1998)].
- 97MI46 J. Liu, *Zhongguo Yiyao Gongye Zazhi* **28**, 514 (1997) [*CA* **128**, 299,626 (1998)].
- 97MI47 O. Cirioni, A. Giacometti, M. Quarta, and G. Scalise, *J. Antimicrob. Chemother.* **40**, 583 (1997).
- 97MI48 C. J. Eboka, S. O. Aigbarboa, and J. O. Akerele, *J. Antimicrob. Chemother.* **39**, 639 (1997).
- 97MI49 F. Li, L. Zhang, H. Jin, J. Gu, R. Fu, and X. Wang, *Fenxi Huaxue* **25**, 644 (1997) [*CA* **127**, 55,984 (1997)].
- 97MI50 N. E. Basci, S. Hanioglu-Kargi, H. Soysal, A. Bozkurt, and S. O. Kayaalp, *J. Pharm. Biomed. Anal.* **15**, 663 (1997).
- 97MI51 F. A. Wong, S. J. Juzwin, and S. C. Flor, *J. Pharm. Biomed. Anal.* **15**, 765 (1997).
- 97MI52 T. Chimura, M. Arai, Y. Onuma, T. Oda, S. Kawagoe, K. Kunii, T. Saito, N. Saito, F. Sato, M. Numasaki, M. Matsuo, K. Murayama, N. Morizaki, *Jpn. J. Antibiol.* **50**, 871 (1997).

- 97MI53 B. Koppenhoefer, U. Epperlein, Z. Xiaofeng, and L. Bingcheng, *Electrophoresis* **18**, 924 (1997).
- 97MI54 P. M. Beringer, P. D. Holtom, and J. P. Rho, *Formulary* **32**, 926 (1997).
- 97MI55 Q. Zang, Z. Bai, and D. Guan, *Yaoxue Xuebao* **32**, 931 (1997) [*CA* **129**, 85,915 (1998)].
- 97MI56 K. Zurbonsen, A. Michel, D. Vittet, P.-A. Bonnet, and C. Chevillard, *Biochem. Pharmacol.* **53**, 1141 (1997).
- 97MI57 S. Zhang, C. He, X. Yu, and X. Wang, *Fenxi Huaxue* **25**, 1177 (1997) [*CA* **128**, 92 (1998)].
- 97MI58 C. Prakash and V. Soliman, *Drug Metab. Dispos.* **25**, 1288 (1997).
- 97MI59 C. Prakash and D. Cui, *Drug Metab. Dispos.* **25**, 1395 (1997).
- 97MI60 A. Nowara, J. Burhenne, and M. Spiteller, *J. Agric. Food Chem.* **45**, 1459 (1997).
- 97MI61 X.-Y. Fu, C.-R. Sun, J.-D. Lu, and Y.-Z. Chen, *Gaodeng Xuexiao Huaxue Xuebao* **18**, 1957 (1997) [*CA* **128**, 53,344 (1998)].
- 97MI62 Y. M. Issa, F. M. Abdel-Gawad, M. A. A. Table, and H. M. Hussein, *Anal. Lett.* **30**, 2071 (1997).
- 97MI63 M. E. Ernst, E. Ernst, and M. E. Klepser, *Am. J. Health-Syst. Pharm.* **54**, 2569 (1997).
- 97MI64 J. L. Bennett, T. Day, L. Feng-Tao, M. Ismail, and A. Farghaly, *Exp. Parasitol.* **87**, 260 (1997).
- 97MIP1 R. Dietrich, G. Sachs, H. Ney, and G. Benedikt, PCT Int. Appl. 97/2020 (1997) [*CA* **126**, 162,299 (1997)].
- 97MIP2 R. Dietrich, G. Sachs, S. Postius, H. Ney, and J. Senn-Bilfinger, PCT Int. Appl. 97/2021 [*CA* **126**, 162,298 (1997)].
- 97MIP3 K. W. Reed and S.-F. Yen, PCT Int. Appl. 97/6782 (1997) [*CA* **126**, 242,892 (1997)].
- 97MIP4 J. Macdonald, J. Matz, and W. Shakespeare, PCT Int. Appl. 97/17,344 (1997) [*CA* **127**, 50,549 (1997)].
- 97MIP5 M. Takemura, Y. Kimura, H. Takahashi, K. Kimura, S. Miyauchi, and H. Ohki, PCT Int. Appl. 97/19072 (1997) [*CA* **127**, 50,550 (1997)].
- 97MIP6 J. A. Fitzgerald, PCT Int. Appl. 97/20,567 (1997) [*CA* **127**, 90,506 (1997)].
- 97MIP7 M. Groh, D. Mccurdy, and F. A. Cabrera, PCT Int. Appl. 97/24,128 (1997) [*CA* **127**, 140,553 (1997)].
- 97MIP8 T. Komai, T. Ohmine, T. Nishigaki, T. Kimura, and T. Katsube, PCT Int. Appl. 97/27856 (1997) [*CA* **127**, 215,196 (1997)].
- 97MIP9 M. E. Selsted, PCT Int. Appl. 97/29765 (1997) [*CA* **127**, 216,752 (1997)].
- 97MIP10 N. Horiuchi, T. Yonezawa, K. Chiba, and H. Yoshida, PCT Int. Appl. 97/31919 (1997) [*CA* **127**, 262,605 (1997)].
- 97MIP11 K. Ikeda, T. Tatsuno, and H. Tanaka, PCT Int. Appl. 97/38,691 (1997) [*CA* **127**, 355,341 (1997)].
- 97MIP12 X. Chen, J. Yuan, and A. Thurkauf, PCT Int. Appl. 97/40,015 (1997) [*CA* **128**, 3611 (1998)].
- 97MIP13 M. Fekete, E. Horváth, I. K. Gyüre, C. Haska-Salamon, P. Arányi, and A. Egyed, Hung. Teljes 75,460 (1997) [*CA* **127**, 303,320 (1997)].
- 97MIP14 S. V. Engashev, Russ. Pat. 2,100,022 (1997) [*CA* **128**, 286,402 (1998)].

- 97MIP15 A. I. Tochilkin and I. R. Kovelman, Russ. Pat. 2,100,359 (1997) [*CA* **128**, 294,784 (1998)].
- 97MIP16 R. Gonzalez-Muñiz, M. T. García-López, I. Gómez-Monterrey, R. Herranz, M. Martín-Martínez, A. M. Barber-Carcamo, Span. Pat. 2,106,683 (1997) [*CA* **129**, 316,545 (1998)].
- 97PHA519 K. Thoma and N. Kubler, *Pharmazie* **52**, 519 (1997).
- 97RCM1879 T. Partanen, P. Vainiotalo, J. Tari, G. Bernáth, and F. Fülöp, *Rapid Commun. Mass Spectrom.* **11**, 1879 (1997).
- 97SL799 C. Agami, D. Bihan, R. Morgentin, and C. Puchot-Kadouri, *Synlett*, 799 (1997).
- 97SL1079 W. I. I. Bakker, O. B. Familoni, J. Padfield, and V. Snieckus, *Synlett*, 1079 (1997).
- 97T5455 T. Billert, R. Beckert, P. Fehling, M. Doering, and H. Goerls, *Tetrahedron* **53**, 5455 (1997).
- 97TA109 C. Louis and C. Hootelé, *Tetrahedron, Asymmetry* **8**, 109 (1997).
- 97TA1855 A. Mazon and C. Najera, *Tetrahedron, Asymmetry* **8**, 1855 (1997).
- 97TAL1271 J. Barbosa, R. Berges, I. Toro, and V. Sanz-Nebot, *Talanta* **44**, 1271 (1997).
- 97USP5677456 N. J. Kim, T. H. Park, M. H. Kim, H. Moon, J. G. Park, and B. J. Kim, U.S. Pat. 5,677,456 (1997) [*CA* **127**, 346,380 (1997)].
- 97USP5703072 P. L. Power and S. Rakhit, U.S. Pat. 5,703,072 (1997) [*CA* **128**, 88,936 (1998)].
- 97USP5703233 P. Bellani, U.S. Pat. 5,703,233 (1997) [*CA* **128**, 88,929 (1998)].
- 98AAC579 M. Tanaka, T. Matsumoto, M. Sakumoto, T. Misao, S. Koichi, K. Takeshi, I. Kabayashi, and J. Kumazawa, *Antimicrob. Agents Chemother.* **42**, 579 (1998).
- 98AAC2359 M. Kinzig-Schippers, U. Fuhr, M. Cesana, C. Muller, A. H. Staib, S. Rietbrock, and F. Sorgel, *Antimicrob. Agents Chemother.* **42**, 2359 (1998).
- 98AF697 V. Majtán and Ľ. Majtánová, *Arzneim.-Forsch.* **48**, 697 (1998).
- 98AHC(69)89 I. Hermecz, *Adv. Heterocycl. Chem.* **69**, 89 (1998).
- 98AHC(70)1 I. Hermecz, *Adv. Heterocycl. Chem.* **70**, 1 (1998).
- 98AHC(71)145 I. Hermecz, *Adv. Heterocycl. Chem.* **71**, 145 (1998).
- 98BMCL725 M. A. Sanner, T. A. Chappie, A. R. Dunaiskis, A. F. Fliri, K. A. Desai, S. H. Zorn, E. R. Jackson, C. G. Johnson, J. M. Morrone, P. A. Saymour, M. J. Majchrzak, W. S. Faraci, J. L. Collins, D. B. Duignan, C. C. DiPrete, J. S. Lee, A. Trozzi, *Bioorg. Med. Chem. Lett.* **8**, 725 (1998).
- 98BMCL2369 R. A. Smith, M. A. Bobko, and W. Lee, *Bioorg. Med. Chem. Lett.* **8**, 2369 (1998).
- 98CPB1021 T. Araki and H. Kitaoka, *Chem. Pharm. Bull.* **46**, 1021 (1998).
- 98CPB1710 K. Kawakami, S. Atarashi, Y. Kimura, M. Takemura, and I. Hayakawa, *Chem. Pharm. Bull.* **46**, 1710 (1998).
- 98EJM763 K. Nishijima, T. Shinkawa, M. Ito, H. Nishida, I. Yamamoto, Y. Onuki, H. Inaba, and S. Miyano, *Eur. J. Med. Chem.* **33**, 763 (1998).
- 98EJOC2461 C. Agami, D. Bihan, L. Hamon, C. Kadouri-Puchot, and M. Lusinch, *Eur. J. Org. Chem.*, 2461 (1998).
- 98EUP856316 S. Sawa, Eur. Pat. 856,316 (1998) [*CA* **129**, 153,245 (1998)].

- 98GEP19652219 U. Petersen, M. Matzke, T. Jaetsch, T. Schenke, T. Himmler, S. Bartel, B. Baasner, H.-O. Werling, K. Schaller, H. Labischinski, and R. Endermann, Ger. Pat. 19,652,219 (1998) [CA 128, 81,718 (1998)].
- 98H(48)1111 I. Hermecz, L. Vasvári-Debreczy, B. Podányi, G. Kereszturi, M. Balogh, Á. Horváth, and P. Várkonyi, *Heterocycles* 48, 1111 (1998).
- 98H(48)2279 J. H. Kim, Y. S. Lee, and C. S. Kim, *Heterocycles* 48, 2279 (1998).
- 98IJC(B)1 B. Laj and E. P. de Souza, *Indian J. Chem. B* 37B, 1 (1998).
- 98JAP(K)98/130149 H. Uchiyama, S. Kurakata, T. Nishigaki, F. Kimura, and T. Katsube, Jpn. Kokai 98/130,149 (1998) [CA 128, 27,962 (1998)].
- 98JAP(K)98/258059 A. Ota, T. Ikei, and T. Suzuki, Jpn. Kokai 98/258,059 (1998) [CA 129, 310,871 (1998)].
- 98JAP(K)98/287669 M. Takemura, H. Takahasi, K. Kawakami, and H. Oki, Jpn. Kokai 98/287,669 (1998) [CA 129, 343,410 (1998)].
- 98JAP(K)98/324631 N. Seki, M. Yamaoka, and K. Tsuji, Jpn. Kokai 98/324,631 (1998) [CA 130, 90,501 (1999)].
- 98JAP(K)98/330205 S. Nishimura and T. Yamaguchi, Jpn. Kokai 98/330,205 (1998) [CA 130, 91,663 (1999)].
- 98JC(A)153 B. Koppenhoefer, U. Epperlein, R. Schlunk, X. Zhu, and B. Lin, *J. Chromatogr. A* 793, 153 (1998).
- 98JC(A)237 G.y. Morovjan, P. Czokan, L. Makranszki, E. A. Abdellah-Nagy, and K. Tóth, *J. Chromatogr. A* 797, 237 (1998).
- 98JC(A)343 G. Carlucci, *J. Chromatogr. A* 812, 343 (1998).
- 98JC(A)411 J. Barbosa, R. Berges, and V. Sanz-Nebot, *J. Chromatogr. A* 823, 411 (1998).
- 98JC(B)87 S. R. Needham, M. J. Cole, and H. G. Fouda, *J. Chromatogr. B* 718, 87 (1998).
- 98JC(B)97 D. H. Wright, V. K. Herman, F. N. Konstantinides, and J. C. Rotschafer, *J. Chromatogr. B* 709, 97 (1998).
- 98JC(B)267 C. Lerch and G. Balschke, *J. Chromatogr. B* 708, 267 (1998).
- 98JHC1349 N. Öcal, Z. Turgut, and S. Kaban, *J. Heterocycl. Chem.* 35, 1349 (1998).
- 98JPS215 G. Zlotos, A. Bucker, M. Kinzig-Schippers, F. Sorgel, and U. Holzgrabe, *J. Pharm. Sci.* 87, 215 (1998).
- 98JPS960 M. Sugawara, Y. Takekuma, H. Yamada, M. Kobayashi, K. Iseki, and K. Miyazaki, *J. Pharm. Sci.* 87, 960 (1998).
- 98LS265 W.-H. Zhu, A. Majluf-Cruz, and G. A. Omburo, *Life Sci.* 63, 265 (1998).
- 98LS953 D. Spina, P. Ferlenga, I. Biasini, E. Moriggi, F. Marchini, C. Semeraro, and C. P. Page, *Life Sci.* 62, 953 (1998).
- 98MI1 M. M. Mabrouk, *Alexandria J. Pharm. Sci.* 12, 1 (1998) [CA 129, 75,916 (1998)].
- 98MI2 O. B. Familoni, *J. Pharm. Res. Dev.* 3, 21 (1998).
- 98MI3 A. Albini, *Rapp. ISTISAN* 23 (1998) [CA 129, 341,260 (1998)].
- 98MI4 A. R. Juvekar and R. V. S. V. Vadlamudi, *Indian J. Pharmacol.* 30, 25 (1998).
- 98MI5 G. Condorelli, L. L. Costanzo, S. Giuffrida, G. De Guidi, S. Sorino, P. Miano, and A. Velardita, *Rapp. ISTISAN* 26 (1998) [CA 129, 341,261 (1998)].
- 98MI6 Y. Du, Z. You, and J. Liao, *Huagong Shikan* 12, 26 (1998) [CA 129, 193,479 (1998)].

- 98MI7 Y. Tong and Q. Wu, *Huaxi Yaoxue Zazhi* **13**, 30 (1998) [*CA* **129**, 293,714 (1998)].
- 98MI8 X. Guo, Q. Wu, J. Yu, K. Dong, and C. Chen, *Guangdong Yaoxueyuan Xuebao* **14**, 33 (1998) [*CA* **129**, 127,279 (1998)].
- 98MI9 S. Zhang, C. He, H. Jin, and X. Wang, *Fenxi Shiyanshi* **17**, 43 (1998) [*CA* **129**, 72,332 (1998)].
- 98MI10 J. Zhang, C. Wang, H. Fan, and J. Pan, *Fenxi Kexue Xuebao* **14**, 45 (1998) [*CA* **128**, 184,743 (1998)].
- 98MI11 M. Huang, J. Sun, G. Li, G. Yang, A. Du, Z. Gao, and J. Wang, *Sepu* **16**, 47 (1998) [*CA* **128**, 188,061 (1998)].
- 98MI12 J. A. Bosso, *J. Infect. Dis. Pharmacother.* **2**, 61 (1998).
- 98MI13 T. Cserhádi, E. Forgács, and Gy. Hajós, *J. Planar Chromatogr.-Mod. TLC* **11**, 64 (1998).
- 98MI14 G. Song, L. Yu, P. Wang, Y. Zhou, and H. Liang, *Shenyang Yaoke Daxue Xuebao* **15**, 65 (1998) [*CA* **129**, 193,788 (1998)].
- 98MI15 F.-A. Wang, I.-L. Jiango, Z. Yan, Z.-C. Wang, and J.-F. Niu, *Microchem. J.* **58**, 67 (1998).
- 98MI16 K. G. Naber, M. Well, K. Hollauer, D. Kirchbauer, and W. Witte, *Chemotherapy (Basel)* **44**, 77 (1998).
- 98MI17 H. Tanaka, H. Yasuda, K.-I. Ohtani, C. Tamamura, A. Kawabe, H. Sakamoto, and M. Nakamura, *Calcium Ion Modulators, Sel. Pap. Satell. Symp.* 1966 (Pub. 1998) 83 [*CA* **130**, 105,145 (1999)].
- 98MI18 M. P. Montanari, M. Prenna, M. Mingoia, S. Ripa, and E. P. Varaldo, *Chemotherapy (Basel)* **44**, 85 (1998).
- 98MI19 Q. Xu, K. Zhu, and M. Ma, *Zhejiang Yike Daxue Xuebao* **27**, 88 (1998) [*CA* **129**, 227,638 (1998)].
- 98MI20 S. K. El-Arini and H. Leuenberger, *Pharm. Acta Helv.* **73**, 89 (1998).
- 98MI21 H. Mikamo, K. Kawazoe, Y. Sato, and T. Tamaya, *Chemotherapy (Basel)* **44**, 99 (1998).
- 98MI22 S. Lee, T. Park, and Y. Lee, *Arch. Pharmacol. Res.* **21**, 106 (1998).
- 98MI23 X. Xu and J. Hu, *Yaowu Fenxi Zazhi* **18**, 114 (1998) [*CA* **129**, 180,224 (1998)].
- 98MI24 B. A. Firestone, M. A. Dickason, and T. Tran, *Int. J. Pharm.* **164**, 119 (1998).
- 98MI25 M. Wang, D. Li, and Y. Long, *Fenxi Kexue Xuebao* **14**, 129 (1998) [*CA* **129**, 58,919 (1998)].
- 98MI26 S. K. Lee, O. H. Park, C. J. Yoon, and D. W. Lee, *J. Microcolumn Sep.* **10**, 133 (1998).
- 98MI27 R. C. Mashru and S. K. Banerjee, *East Pharm.* **41**, 147 (1998).
- 98MI28 J. Silvestre, A. Graul, and J. Castaner, *Drug Future* **23**, 161 (1998).
- 98MI29 W.-Z. Yang, J.-M. Zheng, and J.-S. Hao, *Zhongguo Yiyao Gongye Zazhi* **29**, 161 (1998) [*CA* **129**, 58,724 (1998)].
- 98MI30 W. Xiong, E. Wang, and Z. Tang, *Zhongguo Yaowu Huaxue Zazhi* **8**, 174 (1998) [*CA* **130**, 332,303 (1999)].
- 98MI31 X. Wang, P. Guo, D. Wang, T. Zhou, and L. Ma, *Huaxi Yaoxue Zazhi* **13**, 185 (1998) [*CA* **130**, 213,565 (1999)].
- 98MI32 Q. Meng, X. Guo, and X. Wu, *Guangdong Yaoxueyuan Xuebao* **14**, 186 (1998) [*CA* **129**, 347,354 (1998)].
- 98MI33 E. Pirianowicz-Chaber, D. Marszalek, E. Helbin, and F. Herold, *Acta Pol. Pharm.* **55**, 193 (1998).

- 98MI34 R. S. Mansbach, E. W. Brooks, M. A. Sanner, and S. H. Zorn, *Psychopharmacology (Berlin)* **135**, 194 (1998).
- 98MI35 R. Tang, *Guangdong Yaoxueyuan Xuebao* **14**, 201 (1998) [*CA* **130**, 100,740 (1999)].
- 98MI36 X. Qui, H. Wang, P. Wang, W. Guo, and J. Yu, *Shenyang Yaoka Daxue Xuebao* **15**, 202 (1998) [*CA* **129**, 321,272 (1998)].
- 98MI37 Y. Yang, R. Ji, Z. Hu, and K. Chen, *Yaoxue Xuebao* **33**, 828 (1998) [*CA* **131**, 5239 (1999)].
- 98MI38 B. C. Lin, X. F. Zhu, U. Epperlein, M. Schwiarskott, R. Schlunk, and B. Koppenhoefer, *J. High Resolut. Chromatogr.* **21**, 215 (1998).
- 98MI39 J.-J. Qi, Z.-M. Tian, Z.-R. Li, and H.-Y. Guo, *Zhongguo Yiyao Gongye Zazhi* **29**, 243 (1998) [*CA* **129**, 175,619 (1998)].
- 98MI40 J. A. Hernandez-Arteseros, J. Barbosa, R. Compano, and M. D. Prat, *Chromatographia* **48**, 251 (1998).
- 98MI41 X. Li, H. Xiao, and Z. Sun, *Hunan Nongye Daxue Xuebao* **24**, 251 (1998) [*CA* **129**, 286,928 (1998)].
- 98MI42 D. Wang, X. Wang, P. Guo, L. Ye, and L. Ma, *Huaxi Yaoxue Zazhi* **13**, 256 (1998) [*CA* **130**, 100,764 (1999)].
- 98MI43 P. Gurumurthy, G. Ramachandran, A. K. H. Kumar, P. Venkatesan, V. Chandrasekaran, and P. R. Narayanan, *Indian J. Pharmacol.* **30**, 263 (1998).
- 98MI44 Y. Maruoka, Y. Ohno, H. Tanaka, H. Yasuda, K.-I. Otani, C. Tamamura, and M. Nakamura, *Jpn. J. Pharmacol.* **76**, 265 (1998).
- 98MI45 M. Reda and E.-A. Abd, *Dyes Pigm.* **39**, 267 (1998).
- 98MI46 J. Huang, *Zhongguo Yiyuan Yaoxue Zazhi* **18**, 267 (1998) [*CA* **130**, 115,107 (1999)].
- 98MI47 M.S. Amine, *Egypt. J. Chem.* **41**, 267 [*CA* **130**, 311,755 (1999)].
- 98MI48 J. Yu, J. Lei, and R. Li, *Guangdong Yaoxueyuan Xuebao* **14**, 278 (1998) [*CA* **130**, 201,006 (1999)].
- 98MI49 M. Zheng and J. Qu, *Shenyang Yaoke Daxue Xuebao* **15**, 285 (1998) [*CA* **130**, 52,387 (1999)].
- 98MI50 M. Takamoto, S. Harada, Y. Harada, Y. Kitahara, A. Kajiki, and T. Ishibashi, *Nippon Kagaku Ryoho Gakkai Zasshi* **46**, 303 (1998) [*CA* **129**, 197,549 (1998)].
- 98MI51 D. Zhang, J. Zeng, C. Nianba, and X. Jiang, *Yaowu Fenxi Zazhi* **18**, 308 (1998) [*CA* **130**, 47,069 (1999)].
- 98MI52 K.-H. Choi, M.-C. Baek, B.-K. Kim, and E.-C. Choi, *Arch. Pharmacol. Res.* **21**, 310 (1998).
- 98MI53 S.-Y. Zhang, Z.-H. Wu, Z.-Y. Zhang, and H.-Q. Zuo, *Zhongguo Yiyao Gongye Zazhi* **29**, 315 (1998) [*CA* **129**, 335,846 (1998)].
- 98MI54 X.-Y. Liu, X.-M. Cheng, J.-R. Zhang, S.-Y. Wang, and Z. Hou, *Zhongguo Yiyao Gongye Zazhi* **29**, 319 (1998) [*CA* **129**, 321,278 (1998)].
- 98MI55 S. J. Martin, J. M. Meyer, S. K. Chuek, R. Jung, C. R. Messick, and S. L. Pendland, *Ann. Pharmacother.* **32**, 320 (1998).
- 98MI56 M. Nagao, T. Tsukahara, S. Jaroenpoj, and C. Ardsongnearn, *Shokuhin Eiseigaku Zasshi* **39**, 329 (1998) [*CA* **129**, 315,185 (1998)].
- 98MI57 J. R. Deschamps, C. George, and J. L. Flippen-Anderson, *Lett. Pept. Sci.* **5**, 337 (1998).

- 98MI58 Y. Chen, H. Dong, Q. Dai, and W. Ma, *Zhongguo Kangsengsu Zazhi* **23**, 342 (1998) [*CA* **130**, 291,011 (1999)].
- 98MI59 X. Xu, R.-J. Wu, and B.-C. Lin, *Gaodeng Xuexiao Huaxue Xuebao* **19**, 379 (1998) [*CA* **128**, 265,527 (1998)].
- 98MI60 B. Han, Y. Chen, Y. Chen, and H. Pan, *Zhongguo Yiyuan Yaoxue Zazhi* **18**, 406 (1998) [*CA* **130**, 129,869 (1999)].
- 98MI61 D. Cioli, *Parasitol. Today* **14**, 418 (1998).
- 98MI62 N. Saldou, R. Obernolte, A. Huber, P. A. Baecker, R. Wilhelm, R. Alvarez, B. Li, L. Xia, O. Callan, C. Su, K. Jarnagin, E. R. Shelton, *Cell. Signalling* **10**, 427 (1998).
- 98MI63 R. Gonzalez-Muñiz, I. Gómez-Monterrey, M. Martín-Martínez, R. Herranz, M. T. García-López, A. Barber, S. Ballaz, and J. Del Río, *Pept. 1996 Proc. Eur. Pept. Symp.*, 24<sup>th</sup> (Pub. 1998) 429 [*CA* **130**, 10,300 (1999)].
- 98MI64 S. T. Colgan, M. L. Dumont, and S. G. Ruggeri, *J. Pharm. Biomed. Anal.* **18**, 429 (1998).
- 98MI65 L. Gao, Q. Li, and C. Liu, *Zhongguo Yaoke Daxue Xuebao* **29**, 433 (1998) [*CA* **130**, 301,569 (1999)].
- 98MI66 H. Ma, X. He, and X. Ge, *Zhongguo Yaoke Daxue Xuebao* **29**, 440 (1998) [*CA* **130**, 173,098 (1999)].
- 98MI67 C. Prakash, D. Cui, J. G. Baxter, G. M. Bright, J. Miceli, and K. Wilner, *Drug Metab. Dispos.* **26**, 448 (1998).
- 98MI68 K. Furuhashi, H. Hayakawa, K. Soumi, H. Arai, Y. Watanabe, and H. Narita, *Biol. Pharm. Bull.* **21**, 456 (1998).
- 98MI69 K. Furuhashi, Y. Fukuda, K. Soumi, H. Arai, Y. Watanabe, and H. Narita, *Biol. Pharm. Bull.* **21**, 461 (1998).
- 98MI70 H. L. El-Subbagh and A. A. Al-Badr, *Anal. Profiles Drug Subst. Excipients* **25**, 463 (1998).
- 98MI71 Y. Zhang, *Zhongguo Yaoke Daxue Xuebao* **29**, 470 (1998) [*CA* **130**, 100,750 (1999)].
- 98MI72 H. D. Langtry and H. M. Lamb, *Drugs* **56**, 487 (1998).
- 98MI73 W. S. Faraci, S. H. Zorn, M. A. Sanner, and A. Fliri, *Curr. Opin. Chem. Biol.* **2**, 535 (1998).
- 98MI74 B. Koppenhoefer, U. Epperlein, A. Jakob, S. Wuerthner, Z. Xiaofeng, and L. Bingcheng, *Chirality* **10**, 548 (1998).
- 98MI75 S. K. El-Arini, D. Giron, and H. Leuenberger, *Pharm. Dev. Technol.* **3**, 557 (1998).
- 98MI76 A. Nagai, T. Shibata, M. Nagasawa, N. Shiotani, M. Miyazaki, Y. Kawamura, T. Kodama, and T. Onimaru, *Jpn. J. Antibiot.* **51**, 583 (1998).
- 98MI77 X. Liu, *Yaoxue Xuebao* **33**, 600 (1998) [*CA* **130**, 257,396 (1999)].
- 98MI78 Y. Kawamura, N. Kitou, A. Nagai, T. Sanzen, and T. Kodama, *Jpn. J. Antibiot.* **51**, 600 (1998).
- 98MI79 I. Lazarevic, M. Lelick-Stankov, and P. Djurdjevic, *Main Group Met. Chem.* **21**, 609 (1998).
- 98MI80 S. S. Zhang, H. X. Liu, Z. B. Yuan, and C. L. Yu, *J. Pharm. Biomed. Anal.* **17**, 617 (1998).
- 98MI81 A. Nagai, Y. Kawamura, T. Kodama, and T. Onimaru, *Jpn. J. Antibiot.* **51**, 625 (1998).

- 98MI82 H.-A. Chang, K.-H. Choi, T.-K. Oh, A.-R. Kwon, D.-H. Kim, and E.-C. Choi, *Yakhak Hoechi* **42**, 639 (1998) [*CA* **130**, 107,470 (1999)].
- 98MI83 J. Polonyi, L. Eebringer, J. Dobias, and J. Krajcovic, *Folia Microbiol. (Prague)* **43**, 661 (1998) [*CA* **130**, 63,425 (1999)].
- 98MI84 E. Fasani, A. Profumo, and A. Albini, *Photochem. Photobiol.* **68**, 666 (1998).
- 98MI85 N. Komae, T. Sanzen, T. Kozaki, E. Furubo, Y. Kawamura, and T. Kodama, *Jpn. J. Antibiot.* **51**, 682 (1998).
- 98MI86 B. Fan, W. Yuan, A. Sugii, and K. Oya, *Zhongguo Yaoxue Zazhi (Beijing)* **33**, 693 (1998) [*CA* **130**, 242,387 (1999)].
- 98MI87 V. M. Shinde, B. S. Desai, and N. M. Tendolkar, *Indian Drugs* **35**, 715 (1998).
- 98MI88 C. S. Kim and D. Y. Min, *Arch. Pharmacol. Res.* **21**, 744 (1998).
- 98MI89 T. Kokei, N. Hasegawa, H. Sakai, H. Yamamoto, Y. Yamamoto, H. Yamada, O. Yoshino, M. Yamada, K. Imamura, Y. Yamamoto, and H. Imaizumi, *Iyakuhin Kenkyo* **29**, 779 (1998) [*CA* **130**, 227,628 (1999)].
- 98MI90 F. Zhao, B. Xu, and S. Tong, *Fenxi Huaxue* **26**, 840 (1998) [*CA* **129**, 127,285 (1998)].
- 98MI91 G. Zlotos, M. Oehlmann, P. Nickel, and V. Holzgrabe, *J. Pharm. Biomed. Anal.* **18**, 847 (1998).
- 98MI92 P. Drescher, J. M. Knes, and P. O. Madsen, *Invest. Radiol.* **33**, 858 (1998).
- 98MI93 S. V. Onrust, H. M. Lamb, and J. A. B. Balfour, *Drugs* **56**, 895 (1998).
- 98MI94 D. S. North, D. N. Fish, and J. J. Redington, *Pharmacotherapy* **18**, 915 (1998).
- 98MI95 S. Zhang, Y. Du, and Y. Li, *Fenxi Huaxue* **26**, 915 (1998) [*CA* **129**, 235,704 (1998)].
- 98MI96 K. Furuhashi, Y. Todo, T. Takakura, Y. Watanabe, and H. Narita, *Biol. Pharm. Bull.* **21**, 919 (1998).
- 98MI97 S. Luo, J. Lei, R. Zhang, H. Cai, and R. Li, *Yaoxue Xuebao* **33**, 937 (1998) [*CA* **130**, 119,020 (1999)].
- 98MI98 S. M. Wimer, L. Schoonover, and M. W. Garrison, *Clin. Ther.* **20**, 1049 (1998).
- 98MI99 M. L. Dumont, S. T. Colgan, R. H. Reed, and G. R. Haggan, Jr., *J. Pharm. Biomed. Anal.* **16**, 1075 (1998).
- 98MI100 P. Wang, M. Zhou, Y. Feng, and L. Chen, *Anal. Lett.* **31**, 1523 (1998).
- 98MI101 M. D. Rose, J. Bygrave, and G. W. F. Stubbings, *Analyst (Cambridge U.K.)* **123**, 2789 (1998).
- 98MI102 A. A. El-Shanawani, S. M. El-Adl, and A. E.-A. El-Bayoumi, *Zagazig J. Pharm. Sci.* **7**, 54 (1998) [*CA* **131**, 78,517 (1999)].
- 98MI103 K. H. Kim, S.-I. Park, and B.-Y. Jee, *Gyobyo Kenkyu* **33**, 467 (1998) [*CA* **131**, 13,395 (1999)].
- 98MI104 A. A. Ei-Azm, N. A. Gaafar, A. M. El-Zawahry, and S. A. Fayek, *J. Drug Res.* **22**, 121 (1998).
- 98MI105 Z. Sun, X. Liu, J. Liu, H. Xiao, and Z. Sheng, *Hunan Nongye Daxue Xuebao* **24**, 394 (1998) [*CA* **131**, 153,469 (1999)].
- 98MIP1 S. G. Ruggeri and P. D. Hammen, *PCT Int. Appl.* 98/425 (1998) [*CA* **128**, 114,964 (1998)].



- 98MIP2 T. Mori, M. Tominaga, F. Tabusa, K. Nagami, K. Aba, K. Nakaya, I. Takemura, T. Shinohara, Y. Tanada, and T. Yamauchi, *PCT Int. Appl.* 98/4,536 (1998) [*CA* **128**, 167,413 (1998)].
- 98MIP3 C. M. Harvey, *PCT Int. Appl.* 98/6,407 (1998) [*CA* **128**, 196,680 (1998)].
- 98MIP4 J. R. Fraser, M. H. West, T. J. Krieger, R. Taylor, and D. Erfle, *PCT Int. Appl.* 98/7,745 (1998) [*CA* **128**, 213,381 (1998)].
- 98MIP5 M. Takemura, H. Takashi, and K. Kawakami, *PCT Int. Appl.* 98/13,370 (1998) [*CA* **128**, 244,057 (1998)].
- 98MIP6 H. R. Howard, *PCT Int. Appl.* 98/14,433 (1998) [*CA* **128**, 270,613 (1998)].
- 98MIP7 R. F. Labaudiniere, P. Martres, N. Dodic, and B. A. Dumaitre, *PCT Int. Appl.* 98/16,526 (1998) [*CA* **128**, 294,791 (1998)].
- 98MIP8 B. H. Van Lengerich, *PCT Int. Appl.* 98/18,610 (1998) [*CA* **129**, 8597 (1998)].
- 98MIP9 M. Takemura, H. Takahashi, K. Kimura, R. Miyauchi, H. Ohki, and K. Kawakami, *PCT Int. Appl.* 98/18,783 (1998) [*CA* **129**, 16,131 (1998)].
- 98MIP10 P. Ye, Y. Chen, Y. Shi, F. Shi, J. Li, F. Li, Z. Fu, E. Tian, K. Dong, and W. Li, *Faming Zhuanli Shenqing Gongkai Shuomingshu* 1,197,637 (1998) [*CA* **132**, 255,965 (2000)].
- 98MIP11 G. W. Bemis, F. G. Salituro, J. P. Duffy, J. E. Cochran, E. M. Harrington, M. A. Murcko, K. P. Wilson, and V. P. Galullo, *PCT Int. Appl.* 98/27,098 (1998) [*CA* **129**, 81,749 (1998)].
- 98MIP12 K. F. McClure, *PCT Int. Appl.* 98/34,918 (1998) [*CA* **129**, 175,560 (1998)].
- 98MIP13 M. G. Venet, P. R. Angibaud, Y. A. E. Ligny, V. S. Poncelet, and G. C. Sanz, *PCT Int. Appl.* 98/40,383 (1998) [*CA* **129**, 260,460 (1998)].
- 98MIP14 H. Kashiwase, T. Nishigaki, and T. Katsube, *PCT Int. Appl.* 98/42,341 (1998) [*CA* **129**, 270,603 (1998)].
- 98MIP15 B. Orlek and P. Ainsworth, *PCT Int. Appl.* 98/45,293 (1998) [*CA* **129**, 302,652 (1998)].
- 98MIP16 S. M. Sebt, A. D. Hamilton, D. J. Augeri, K. J. Barr, B. G. Donner, S. A. Fakhoury, D. A. Janowick, D. M. Kalvin, J. J. Larsen, G. Liu, S. J. O'Connor, S. H. Rosenberg, W. Shen, R. E. Swenson, B. K. Sorensen, G. M. Sullivan, B. G. Szczepankiewicz, A. S. Tasker, J. I. Wasick, and M. Winn, *PCT Int. Appl.* 98/50,029 (1998) [*CA* **130**, 25,338 (1999)].
- 98MIP17 M. Takemura, H. Takahashi, K. Sugita, H. Ohki, S. Miyauchi, and R. Miyauchi, *PCT Int. Appl.* 98/52,939 (1998) [*CA* **130**, 13,992 (1999)].
- 98MIP18 P. A. Carpino, D. A. Griffith, and B. A. Lefker, *PCT Int. Appl.* 98/58,947 (1998) [*CA* **130**, 95,849 (1999)].
- 98MIP19 Y. Yang, R. Ji, K. Chen, and H. Jiang, *Faming Zhuanli Shenqing Gongkai Shuomingshu* 1,181,381 (1998) [*CA* **132**, 265,211 (2000)].
- 98MIP20 H. Zhou, *Faming Zhuanli Shenqing Gongkai Shuomingshu* 1,190,002 (1998) [*CA* **132**, 199,043 (2000)].
- 98RCM1216 F. Beaudry, J. C. Y. Le Blanc, M. Coutu, and N. K. Brown, *Rapid Commun. Mass Spectrom.* **12**, 1216 (1998).
- 98T2529 U. Lindemann, G. Reck, D. Wulff-Molder, and P. Wessing, *Tetrahedron* **54**, 2529 (1998).

- 98T7395 J. H. Kim, Y. S. Lee, H. Park, and C. S. Kim, *Tetrahedron* **54**, 7395 (1998).
- 98T10309 C. Agami, D. Bihan, L. Hamon, and C. Puchot-Kadouri, *Tetrahedron* **54**, 10,309 (1998).
- 98T13505 H. Takahata, Y. Yotsui, and T. Momose, *Tetrahedron* **54**, 13,505 (1998).
- 98TAL83 M. Rizk, F. Belal, F. A. Aly, and N. M. El-Enany, *Talanta* **46**, 83 (1998).
- 98TL3659 J. D. Scott, T. N. Tippie, and R. M. Williams, *Tetrahedron Lett.* **39**, 3659 (1998).
- 98TL7021 B. B. Snider and C. Xie, *Tetrahedron Lett.* **39**, 7021 (1998).
- 98TL7239 K. E. Frank and J. Aubé, *Tetrahedron Lett.* **39**, 7239 (1998).
- 98USP5854227 J. F. Hartmann and D. Farcasiu, U.S. Pat. 5,854,227 (1998) [CA **130**, 90,529 (1999)].
- 99AF557 H. Feldmeier and L. Chitsulo, *Arzneim. Forsch.* **49**, 557 (1999).
- 99AP19 H. I. El-Subbagh, A. H. Abadi, I. E. Al-Khawad, and K. A. Al-Rashood, *Arch. Pharm. (Weinheim, Ger.)* **332**, 19 (1999).
- 99AX(C)1950 I. Wolska and F. Herold, *Acta Crystallogr. C* **55**, 1950 (1999).
- 99BMC2525 P. Manini, M. d'Ischia, R. Lanzetta, M. Parrilli, and G. Prota, *Bioorg. Med. Chem.* **7**, 2525 (1999).
- 99BMCL2621 R. J. DeVita, M. T. Goulet, M. J. Wyvratt, M. H. Fisher, J.-L. Lo, Y. T. Yang, K. Cheng, and R. G. Smith, *Bioorg. Med. Chem. Lett.* **9**, 2621 (1999).
- 99BMCL3063 M. Hagihara, H. Kashiwase, T. Katsube, T. Kimura, T. Komai, K. Momota, T. Ohmine, T. Nishigaki, S. Kimura, K. Shimada, *Bioorg. Med. Chem. Lett.* **9**, 3063 (1999).
- 99CPB1629 P. de la Torre, S. Torrado, and S. Torrado, *Chem. Pharm. Bull.* **47**, 1629 (1999).
- 99EUP893453 F.-T. A. Chen, G. G. Y. Shen, R. A. Evangelista, and C. S. Oh, Eur. Pat. 893,453 (1999) [CA **130**, 158,525 (1999)].
- 99EUP894796 G. Guillaumet, J.-Y. Merour, F. Touzeau, B. Pfeiffer, P. Renard, and E. Scalbert, Eur. Pat. 894,796 (1999) [CA **130**, 139,351 (1999)].
- 99GEP19802239 S. Bartel, W. Guarnieri, D. Haebich, S. Raddatz, B. Riedl, U. Rosentreter, M. Ruppelt, A. Stolle, H. Wild, R. Endermann, and H.-P. Kroll, Ger. Offen 19,802,239 (1999) [CA **131**, 129,999 (1999)].
- 99H(51)1499 A. Profumo, E. Fasani, and A. Albini, *Heterocyclic* **51**, 1499 (1999).
- 99H(51)1563 J. Adrio, J. C. Carretero, J. L. G. Ruano, A. Pallarès, and M. Vicioso, *Heterocycles* **51**, 1563 (1999).
- 99H(51)2065 O. Froelich, F. Cossart, M. Bonin, J.-C. Quirion, and H.-P. Husson, *Heterocycles* **51**, 2065 (1999).
- 99JA2651 D. L. Comins, J. T. Kueth, H. Hong, and F. J. Lakner, *J. Am. Chem. Soc.* **121**, 2651 (1999).
- 99JAP(K)99/12278 T. Yamamoto, M. Fukuari, H. Okada, K. Chiba, and H. Yoshida, Jpn. Kokai 99/12,278 (1999) [CA **130**, 124,998 (1999)].
- 99JAP(K)99/60485 T. Hirasawa, Jpn. Kokai 99/60,485 (1999) [CA **130**, 218,260 (1999)].
- 99JAP(K)99/92309 A. Nakagawa, Y. Hatakeyama, and S. Enomoto, Jpn. Kokai 99/92,309 (1999) [CA **130**, 291,575 (1999)].
- 99JAP(K)99/147883 M. Fujita, K. Chiba, and H. Yoshida, Jpn. Kokai 99/147,883 (1999) [CA **131**, 31,880 (1999)].

- 99JAP(K)99/222431 T. Mori, M. Tominaga, F. Tabusa, K. Ei, K. Abe, K. Nakaya, I. Takemura, T. Shinohara, Y. Tanada, and T. Yamauchi, *Jpn. Kokai* 99/222,431 (1999) [*CA* **131**, 189,691 (1999)].
- 99JBC4839 J. M. Atienza, D. Susanto, C. Huang, A. S. McCarty, and J. Colicelli, *J. Biol. Chem.* **274**, 4839 (1999).
- 99JC(A)253 P.h. Schmitt-Kopplin, J. Burhenne, D. Freitag, M. Spiteller, and A. Kettrup, *J. Chromatogr. A* **837**, 253 (1999).
- 99JC(B)151 S. Zeng, J. Zhong, L. Pan, and Y. Li, *J. Chromatogr. B* **728**, 151 (1999).
- 99JHC389 F. Herold, I. Wolska, E. Helbin, M. Król, and J. Kleps, *J. Heterocycl. Chem.* **36**, 389 (1999).
- 99JLC281 S.-W. Sun and A.-C. Wu, *J. Liq. Chromatogr. Relat. Technol.* **22**, 281 (1999).
- 99JLC1813 P. S. Bonato, V. L. Lanchote, R. Bortocan, V. A. P. Jabor, F. O. Paías, E. Ricci-Junior, and R. Carvalho, *J. Liq. Chromatogr. Relat. Technol.* **22**, 1813 (1999).
- 99JLC2225 J. C. Spell and J. T. Stewart, *J. Liq. Chromatogr. Relat. Technol.* **22**, 2225 (1999).
- 99JOC3790 H. Ohtake, Y. Imada, and S.-I. Murahashi, *J. Org. Chem.* **64**, 3790 (1999).
- 99JOC5388 E. Fasani, F. F. Barberis Negra, M. Mella, S. Monti, and A. Albini, *J. Org. Chem.* **64**, 5388 (1999).
- 99JOC6041 P. A. Grieco and M. D. Kaufman, *J. Org. Chem.* **64**, 6041 (1999).
- 99JOC8402 M. David, H. Dhimane, C. Vanucci-Bacqué, and G. Lhommet, *J. Org. Chem.* **64**, 8402 (1999).
- 99JOC9001 J. Valenciano, A. M. Cuadro, J. J. Vaquero, J. Alvarez-Builla, R. Palmeiro, and O. Castaño, *J. Org. Chem.* **64**, 9001 (2000).
- 99JPP905 I. Mahmood, *J. Pharm. Pharmacol.* **51**, 905 (1999).
- 99JPR332 T. Billert, R. Beckert, M. Döring, and H. Görls, *J. Prakt. Chem. (Weinheim, Ger.)* **341**, 332 (1999).
- 99JPR37 E. Fanghänel and Th. Lochter, *J. Prakt. Chem.* **341**, 37 (1999).
- 99MI1 J. Mitsuyama, S. Miyazaki, Y. Ishii, T. Matsumoto, K. Tateda, Y. Kaneko, and K. Yamaguchi, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 1 (1999) [*CA* **130**, 349,621 (1999)].
- 99MI2 M. R. C. G. Novaes, J. P. De Souza, and H. C. De Araujo, *Quin. Nova* **22**, 5 (1999) [*CA* **130**, 196,623 (1999)].
- 99MI3 K. Tanaka, N. Kato, H. Kato, and K. Watanabe, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 16 (1999) [*CA* **130**, 349,622 (1999)].
- 99MI4 H. Mikamo, Y. Sato, Y. Hayasaki, K. Kawazoe, K. Izumi, K. Ito, Y. Yamada, and T. Tamaya, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 21 (1999) [*CA* **130**, 349,623 (1999)].
- 99MI5 W. Zhou, J. Liu, A. Yu, X. Chen, and X. Zhang, *J. Chin. Pharm. Sci.* **8**, 21 (1999) [*CA* **130**, 352,234 (1999)].
- 99MI6 K. Suzuki, Y. Aoki, Y. Kido, A. Tsuji, K. Ito, and M. Maeda, *Shokuhin Eiseigaku Zasshi* **40**, 23 (1999) [*CA* **130**, 222,298 (1999)].
- 99MI7 T. Nishino, Y. Ikeda, M. Otsuki, H. Hayashi, and R. Imanishi, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 25 (1999) [*CA* **130**, 349,624 (1999)].
- 99MI8 L. Jiang and Y. Zheng, *Zhongguo Yiyuan Yaoxue Zazhi* **19**, 29 (1999) [*CA* **130**, 191,362 (1999)].

- 99MI9 J. Mitsuyama, M. Takahata, Y. Yamishiro, R. Kitayama, T. Muratani, N. Matsumura, T. Fukuta, M. Nakata, H. Yamada, J. Maehana, S. Hamada, H. Sugiyama, M. Shimakura, S. Minami, Y. Watanabe, and H. Narita, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 37 (1999) [*CA* **130**, 349,625 (1999)].
- 99MI10 R. Tan, M. Mo, and G. Li, *Huaxi Yaoxue Zazhi* **14**, 45 (1999) [*CA* **130**, 272,091 (1999)].
- 99MI11 L. J. V. Piddock, Y.-F. Jin, V. Ricci, and A. E. Asuquo, *J. Antimicrob. Chemother.* **43**, 61 (1999).
- 99MI12 H. Mikamo, Y. Sato, Y. Hayasaki, K. Kawazoe, and T. Tamaya, *Chemotherapy (Basel)* **45**, 154 (1999).
- 99MI13 X. He, G. Cao, L. Liu, C. Sun, and Y. Song, *Zhongguo Yaoxue Zazhi (Beijing)* **34**, 183 (1999) [*CA* **130**, 272,118 (1999)].
- 99MI14 A. I. Azcurra, L. M. Yudi, and A. M. Baruzzi, *J. Electroanal. Chem.* **461**, 194 (1999).
- 99MI15 B. A. Lipsky and C. A. Baker, *Clin. Infect. Dis.* **28**, 352 (1999).
- 99MI16 T. Perez-Ruiz, C. Martinez-Lozano, A. Sanz, and E. Bravo, *Chromatographia* **49**, 419 (1999).
- 99MI17 P. T. Djurdjevic and M. Jelikic-Stankov, *J. Pharm. Biomed. Anal.* **19**, 501 (1999).
- 99MI18 M. Sakai, A. Hara, S. Anjo, and M. Nakamura, *J. Pharm. Biomed. Anal.* **18**, 1057 (1999).
- 99MI19 I.-Y. Choi, J.-Y. Son, and K.-H. Chung, *Bull. Korean Chem. Soc.* **20**, 484 (1999).
- 99MI20 J. M. O'Donnell and S. Frith, *Pharmacol., Biochem. Behav.* **63**, 185 (1999).
- 99MI21 J. E. Souness, C. Houghton, N. Sardar, and M. T. Withnall, *Biochem. Pharmacol.* **58**, 991 (1999).
- 99MI22 N. Aoki, Y. Usuda, Y. Isizuka, N. Wakabayashi, S. Hayashi, Y. Honma, and N. Kitamura, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 204 (1999) [*CA* **131**, 166 (1999)].
- 99MI23 Y. Yang, R. Ji, K. Chen, H. Ye, and J. Wu, *Yaoxue Xuebao* **34**, 349 (1999) [*CA* **132**, 58,727 (2000)].
- 99MI24 H. Ye, J.-M. Wu, Y.-S. Yang, R.-Y. Ji, and K.-X. Chen, *Zhongguo Yaoli Xuebao* **20**, 1031 (1999) [*CA* **132**, 75,906 (1999)].
- 99MI25 M.-L. Liu and H.-Y. Guo, *Zhongguo Yiyao Gongye Zazhi* **30**, 472 (1999) [*CA* **132**, 122,529 (2000)].
- 99MI26 W. Li, Y.-D. Ban, Y. Sha, and L.-J. Wu, *Zhongguo Yiyao Gongye Zazhi* **30**, 407 (1999) [*CA* **132**, 237,231 (2000)].
- 99MI27 K. Furuhashi, N. Terashima, S. Ono, K. Tanaka, H. Fukuda, H. Nagasawa, N. Nojima, and H. Arai, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 104 (1999) [*CA* **131**, 268 (1999)].
- 99MI28 K. Furuhashi, N. Terashima, S. Ono, K. Tanaka, H. Fukuda, H. Nagasawa, N. Nojima, and H. Arai, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 118 (1999) [*CA* **131**, 269 (1999)].
- 99MI29 M. Ohmichi and Y. Hiraga, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 196 (1999) [*CA* **131**, 270 (1999)].
- 99MI30 M. Nakashima, K. Uemura, K. Kosuge, and T. Uematsu, *Nippon Kagaku Ryoho Gakkai Zasshi* **47** (Suppl. 1), 141 (1999) [*CA* **131**, 165 (1999)].

- 99MI31 X. F. Zhu, Y. S. Ding, B. C. Lin, A. Jakob, and B. Koppenhoefer, *Electrophoresis* **20**, 1869 (1999).
- 99MI32 F. Belal, M. Rizk, F. A. Aly, and N. M. El-Enany, *Chem. Anal. (Warsaw)* **44**, 763 (1999) [*CA* **131**, 161,714 (1999)].
- 99MI33 X. F. Zhu, B. C. Lin, A. Jakob, S. Wuerthner, and B. Koppenhoefer, *Electrophoresis* **20**, 1878 (1999).
- 99MI34 W. Wang, X. Y. Fu, and Y. Z. Chen, *Chin. Chem. Lett.* **10**, 831 (1999) [*CA* **132**, 54,939 (2000)].
- 99MI35 H. Hopkala and D. Kowalczyk, *Acta Pol. Pharm.* **57**, 3 (1999).
- 99MI36 Y.-S. Yang, R.-Y. Ji, and K.-X. Chen, *Chin. J. Chem.* **17**, 539 (1999) [*CA* **132**, 22,935 (2000)].
- 99MI37 G. Condorelli, G. De Guidi, S. Giuffrida, S. Sortino, R. Chillemi, and S. Sciuto, *Photochem. Photobiol.* **70**, 280 (1999).
- 99MI38 J. B. Atkins, J. Chlan-Fourney, H. E. Nye, N. Hiroi, W. A. Carlezon, Jr., and E. J. Nestler, *Synapse (N.Y.)* **33**, 118 (1999).
- 99MI39 F.-T. A. Chen and R. A. Evangelista, *J. Chin. Chem. Soc. (Taipei)* **46**, 847 (1999) [*CA* **132**, 26,956 (2000)].
- 99MI40 Z. G. Alier, O. P. Krasnykh, A. N. Maslivets, Yu.S. Andreichikov, and L. O. Atovmian, *Russ. Chem. Bull.* **48**, 2131 (1999).
- 99MI41 W. Jiang, D. Liang, M. Liang, L. Xu, Y. Huang, J. Miao, Y. Qin, Q. Yu, and Y. Zou, *Zhongguo Kangshengsu Zazhi* **24**, 377 (1999) [*CA* **132**, 329,391 (2000)].
- 99MI42 S. Sortino, G. Marconi, S. Giuffrida, G. De Guidi, and S. Monti, *Photochem. Photobiol.* **70**, 731 (1999).
- 99MI43 G. Becket, L. J. Schep, and M. Y. Tan, *Int. J. Pharm.* **179**, 65 (1999).
- 99MI44 K. Frenzel, L. Grigull, E. Odongo-Aginya, C. M. Ndugwa, T. Loroni-Lakwo, U. Schweigmann, U. Vester, N. Spannbrucker, and E. Doehring, *Am. J. Trop. Med. Hyg.* **60**, 927 (1999).
- 99MI45 L. Maggi, E. O. Machiste, M. L. Torre, and U. Conte, *Eur. J. Pharm. Biopharm.* **48**, 37 (1999).
- 99MI46 A. Armson, B. P. Meloni, J. A. Reynoldson, and R. C. A. Thompson, *FEMS Microbiol. Lett.* **178**, 227 (1999).
- 99MI47 L. Veerakumari and N. Munuswamy, *Cytobios* **98**, 39 (1999).
- 99MI48 J. Martinez, J. Perez-Serrano, J. Perez-Serrano, W. E. Bernadina, and F. Rodriguez-Caabeiro, *Exp. Parasitol.* **93**, 171 (1999).
- 99MI49 S. V. P. Malheiros, N. C. Meirelles, and P. L. O. Volpe, *Thermochim. Acta* **328**, 121 (1999).
- 99MI50 M. Ismail, S. Botros, A. Metwally, S. William, A. Farghally, L.-F. Tao, T. A. Day, and J. L. Bennett, *Am. J. Trop. Med. Hyg.* **60**, 932 (1999).
- 99MI51 S. Xiao, J. Chollet, M. Booth, N. A. Weiss, and M. Tanner, *Trans. R. Soc. Trop. Med. Hyg.* **93**, 324 (1999).
- 99MI52 G. Hancu and A. Gyeresi, *Farmacia (Bucharest)* **47**, 11 (1999) [*CA* **132**, 284,326 (2000)].
- 99MI53 Y. Yu, S. Yan, X. Hu, H. Jin, X. Wang, and C. Zhuo, *Huaxi Yaoxue Zazhi* **14**, 315 (1999) [*CA* **132**, 325,958 (2000)].
- 99MI54 H.-W. Zhang, *Zhongguo Yiyao Gongye Zazhi* **30**, 238 (1999) [*CA* **131**, 9692 (1999)].
- 99MI55 Y. H. Moon, S. B. Kang, B. Y. Chung, and Y. Kim, *Korean J. Med. Chem.* **9**, 12 (1999) [*CA* **131**, 144,566 (1999)].

- 99MI56 Y. Yang, R. Ji, Z. Hu, K. Chen, and J. Wu, *Yaoxue Xuebao* **34**, 197 (1999) [*CA* **131**, 153,420 (1999)].
- 99MI57 S. C. Dhanesar, *J. Planar Chromatogr.* **12**, 280 (1999).
- 99MI58 Y. Yang, R. Ji, K. Chen, and J. Ding, *Yaoxue Xuebao* **34**, 119 (1999) [*CA* **131**, 110,880 (1999)].
- 99MI59 Y. Chen, S. Liu, and H. Dong, *Zhongguo Kangshengsu Zazhi* **24**, 290 (1999) [*CA* **132**, 73,155 (2000)].
- 99MI60 F. Sorgel, M. Kinzig-Schippers, C. Sauber, and J. Bulitta, *Chemother. J.* **8** (Suppl.), 19 (1999).
- 99MI61 C. Hu, J. Jiang, and D. Gu, *Yaowu Fenxi Zazhi* **19**, 371 (1999) [*CA* **132**, 227,525 (2000)].
- 99MI62 M. V. Shul'gina, N. I. Fadeeva, T. N. Bol'shakova, I. B. Levshin, and R. G. Glushkov, *Pharm. Chem. J.* **33**, 348 (1999).
- 99MI63 C. Hu, D. Gu, G. Chang, J. Jiang, and S. Jin, *Yaoxue Xuebao* **34**, 848 (1999) [*CA* **132**, 325,921 (2000)].
- 99MI64 G. De Guidi, S. Giuffrida, S. Monti, P. S. Pisu, S. Sortino, and L. L. Costanzo, *Int. J. Photoenergy* **1**, 13 (1999).
- 99MIP1 M. F. Saettone, B. Giannaccini, E. Boldrini, and P. Bianchini, *PCT Int. Appl.* 99/4823 [*CA* **130**, 158,394 (1997)].
- 99MIP2 T. H. Park, Y. H. Ha, and D. Y. Jeong, *PCT Int. Appl.* 99/7706 (1999) [*CA* **130**, 182,368 (1999)].
- 99MIP3 M. B. Gravestock, *PCT Int. Appl.* 99/10,342 (1999) [*CA* **130**, 209,696 (1999)].
- 99MIP4 N. Horiuchi, T. Yonozawa, K. Chiba, and H. Yoshida, *PCT Int. Appl.* 99/10,351 (1999) [*CA* **130**, 196,646 (1999)].
- 99MIP5 B. Leroux and S. K. Huber, *PCT Int. Appl.* 99/18,796 (1999) [*CA* **130**, 278,023 (1999)].
- 99MIP6 J.-F. Patoiseau, E. Dupont-Passelaigue, and W. Koek, *PCT Int. Appl.* 99/20,622 (1999) [*CA* **130**, 296,700 (1999)].
- 99MIP7 T. Komai, T. Ohmine, H. Furukawa, M. Ishimura, T. Agatsuma, Y. Kuroki, and T. Katsube, *PCT Int. Appl.* 99/33,835 (1999) [*CA* **131**, 87,919 (1999)].
- 99MIP8 S. Maddaford, T. Xin, A. Slassi, and A. Tehim, *PCT Int. Appl.* 99/65,906 (1999) [*CA* **132**, 49,982 (2000)].
- 99MIP9 G. M. Bright, *PCT Int. Appl.* 99/52,907 (1999) [*CA* **131**, 299,376 (1999)].
- 99MIP10 S. M. Bromidge and H. T. Serafinowska, *PCT Int. Appl.* 99/42,465 (1999) [*CA* **131**, 170,364 (1999)].
- 99MIP11 A. M. M. Mjalli, J. C. Mason, K. L. Arienti, K. M. Short, R. D. A. Kimmich, and T. K. Jones, *PCT Int. Appl.* 99/47,549 (1999) [*CA* **131**, 243,287 (1999)].
- 99MIP12 H. Suzuki, H. Ogawa, K. Ueno, and M. Takeuchi, *PCT Int. Appl.* 99/63,968 (1999) [*CA* **132**, 26,867 (2000)].
- 99S704 R. Chinchilla, N. Galindo, and C. Nájer, *Synthesis*, 704 (1999).
- 99SL1094 C. Agami, S. Comesse, C. Kadouri-Puchot, and M. Lusinch, *Synlett*, 1094 (1999).
- 99T7915 P. Puebla, Z. Honores, M. Medarde, L. Morán, E. Caballero, and A. San Feliciano, *Tetrahedron* **55**, 7915 (1999).
- 99TL763 J. Valenciano, A. M. Cuadro, J. J. Vaquero, and J. Alvarez-Builla, *Tetrahedron Lett.* **40**, 763 (1999).

- 99TL1211 S. W. Jones, C. F. Palmer, J. M. Paul, and P. D. Tiffin, *Tetrahedron Lett.* **40**, 1211 (1999).
- 99TL3699 A. Zaparucha, M. Danjoux, A. Chiaroni, J. Royer, and H.-P. Husson, *Tetrahedron Lett.* **40**, 3699 (1999).
- 99USP5952494 Y. Kim, S. B. Kang, and S. Park, U.S. Pat. 5,952,494 (1999) [CA **131**, 184,954 (1999)].
- 00AAC73 M. V. Moretti, S. Pauluzzi, and M. Cesana, *Antimicrob. Agents Chemother.* **44**, 73 (2000).
- 00AAC2126 K. Kawakami, K. Namba, M. Tanaka, N. Matsushashi, K. Sato, and M. Takemura, *Antimicrob. Agents Chemother.* **44**, 2126 (2000).
- 00AAC2764 R. Gozalbes, M. Brun-Pascaud, R. Garcia-Domenech, J. Galvez, P.-M. Girard, J.-P. Doucet, and F. Derouin, *Antimicrob. Agents Chemother.* **44**, 2764 (2000).
- 00AAC2771 R. Gozalbes, M. Brun-Pascaud, R. Garcia-Domenech, J. Galvez, P.-M. Girard, J.-P. Doucet, and F. Derouin, *Antimicrob. Agents Chemother.* **44**, 2771 (2000).
- 00BJP655 D. Morin, R. Sapena, A. Elimadi, B. Testa, S. Labidalle, A. Le Ridant, and J.-P. Tillement, *Br. J. Pharmacol.* **130**, 655 (2000).
- 00BMC523 B. Herberich, J. D. Scott, and R. M. Williams, *Bioorg. Med. Chem.* **8**, 523 (2000).
- 00BMCL2033 C. de Gregorio Alapont, R. Garcia-Domenech, J. Gálvez, M. J. Ros, S. Wolski, and M. D. Garcia, *Bioorg. Med. Chem. Lett.* **10**, 2033 (2000).
- 00CHE615 A. N. Maslivets, O. V. Golovkina, O. P. Krasnykh, and Z. G. Aliev, *Chem. Heterocycl. Compd. (Engl. Transl.)* **36**, 615 (2000).
- 00GEP19854402 H. Jomaa, Ger. Offen 19,854,402 (2000) [CA **133**, 785 (2000)].
- 00HCA349 C.-L. Tzeng, I.-L. Chen, Y.-L. Chen, T.-C. Wang, Y.-L. Chang, and C.-M. Teng, *Helv. Chim. Acta* **83**, 349 (2000).
- 00JA4583 H. Abe, S. Aoyagi, and C. Kibayashi, *J. Am. Chem. Soc.* **122**, 4583 (2000).
- 00JA5017 C. Xie, M. T. C. Runnegar, and B. B. Snider, *J. Am. Chem. Soc.* **122**, 5017 (2000).
- 00JA11009 P. A. Evans, T. Manangan, and A. L. Rheingold, *J. Am. Chem. Soc.* **122**, 11,009 (2000).
- 00JAP(K)00/86659 N. Tamura, M. Kawamura, and S. Kitamura, Jpn. Kokai 00/86,659 (2000) [CA **132**, 246,361 (2000)].
- 00JAP(K)00/169395 G. Chan and E. S. Hamanaka, Jpn. Kokai, 00/169,395 (2000) [CA **133**, 38,245 (2000)].
- 00JAP(K)00/302698 Y. Oda, Jpn. Kokai 00/302,698 (2000) [CA **133**, 335,024 (2000)].
- 00JBC30069 G. Jedlitschky, B. Burchell, and D. Keppler, *J. Biol. Chem.* **275**, 30,069 (2000).
- 00JC(A)295 T. Horimai, T. Arai, and Y. Sato, *J. Chromatogr. A* **875**, 295 (2000).
- 00JC(B)221 H. Meier and G. Balschke, *J. Chromatogr. B* **748**, 221 (2000).
- 00JC(B)255 M. Hernandez, F. Borrull, and M. Calull, *J. Chromatogr. B: Biomed. Sci. Appl.* **742**, 255 (2000).
- 00JMC609 M. C. Chrystelis, E. A. Rekka, and P. N. Kourounakis, *J. Med. Chem.* **43**, 609 (2000).
- 00JMC1109 N. Baurin, E. Vangrevelinghe, L. Morin-Allory, J.-Y. Mérour, P. Renard, M. Payard, G. Guillaumet, and C. Marot, *J. Med. Chem.* **43**, 1109 (2000).

- 00JMC2204 P. Crivori, G. Cruciani, P.-A. Carrupt, and B. Testa, *J. Med. Chem.* **43**, 2204 (2000).
- 00JOC655 K. E. Frank and J. Aubé, *J. Org. Chem.* **65**, 655 (2000).
- 00JOC3771 B. T. Smith, V. Garcias, and J. Aubé, *J. Org. Chem.* **65**, 3771 (2000).
- 00JOC4435 C. Agami, S. Comesse, and C. Kadouri-Puchot, *J. Org. Chem.* **65**, 4435 (2000).
- 00JPO213 F. Herold, D. Maciejewska, and I. Wolska, *J. Phys. Org. Chem.* **13**, 213 (2000).
- 00JPS79 M. A. Etman, *J. Pharm. Sci.* **14**, 79 (2000).
- 00JPS128 Y. Gou, S. R. Byrn, and G. Zograf, *J. Pharm. Sci.* **89**, 128 (2000).
- 00JST73 D. Maciejewska, F. Herold, and I. Wolska, *J. Mol. Struct.* **553**, 73 (2000).
- 00MI1 D. Wu, Y. Sun, R. Zhang, and H. Cai, *Huaxi Yaoxue Zazhi* **15**, 103 (2000) [*CA* **132**, 329,370 (2000)].
- 00MI2 C. Fierens, S. Hillaert, and W. Van der Bossche, *J. Pharm. Biomed. Anal.* **22**, 763 (2000).
- 00MI3 J. Yu, Y. Yan, J. Lei, and W. Yin, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 29 (2000) [*CA* **132**, 171,240 (2000)].
- 00MI4 S. Yang, G. Zhao, and D. Wang, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 88 (2000) [*CA* **132**, 242,038 (2000)].
- 00MI5 H.-Y. Liao and F. Shen, *Zhongguo Yiyao Gongye Zazhi* **31**, 170 (2000) [*CA* **132**, 352,887 (2000)].
- 00MI6 S. V. P. Malheiros, N. C. Meirelles, and E. de Paula, *Biophys. Chem.* **83**, 89 (2000).
- 00MI7 D. C. Hooper, *Clin. Infect. Dis.* **30**, 243 (2000).
- 00MI8 T. Sugiyama, R. Matsuyama, S. Usui, Y. Katagiri, and K. Hirano, *Biol. Pharm. Bull.* **23**, 274 (2000).
- 00MI9 Q. Zhu, G. Ma, Q. Deng, and L. Zeng, *Fenxi Huaxue* **28**, 349 (2000) [*CA* **132**, 326,141 (2000)].
- 00MI10 Y. Rao, Y. Tong, X. Zhang, G. Luo, and W. R. G. Baeyens, *Anal. Lett.* **33**, 1117 (2000).
- 00MI11 H.-R. Park, H.-C. Lee, T. H. Kim, J.-K. Lee, K. Yang, and K.-M. Bark, *Photochem. Photobiol.* **71**, 281 (2000).
- 00MI12 M. H. Abo-Ghalia and A. M. Soliman, *Acta Pol. Pharm.* **57**, 53 (2000).
- 00MI13 X. Chen, L. Yang, and H. Zou, *Fenxi Huaxue* **28**, 879 (2000) [*CA* **133**, 171,580 (2000)].
- 00MI14 Z. Liu, J. Ji, and F. He, *Shenyang Yaoke Daxue Xuebao* **17**, 52 (2000) [*CA* **133**, 63,839 (2000)].
- 00MI15 P. Ball, *J. Antimicrob. Chemother.* **45**, 557 (2000).
- 00MI16 C. Yang, N. Mei, and C. Yang, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 216 (2000) [*CA* **133**, 94,648 (2000)].
- 00MI17 Y. Rao, Y. Tong, X. Zhang, G. Luo, and W. R. G. Baeyens, *Anal. Chim. Acta* **416**, 227 (2000).
- 00MI18 P. Liang, Y.-C. Qin, Z.-C. Jiang, and C.-M. Xiong, *Fenxi Shiyanshi* **19**, 56 (2000) [*CA* **133**, 110,096 (2000)].
- 00MI19 C. H. Nightingale, E. M. Grant, and R. Quintiliani, *Chemotherapy (Basel)* **40** (Suppl. 1), 6 (2000).
- 00MI20 W. Luo, *Guangdong Weiliang Yuansu Kexue* **7**, 64 (2000) [*CA* **133**, 140,347 (2000)].
- 00MI21 X. Xu, J. Luo, Y. Zhang, H. Du, and C. Lei, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 413 (2000) [*CA* **133**, 155,554 (2000)].



- 00M122 Q. Gong, W. Jin, and C. Dong, *Fenxi Huaxue* **28**, 672 (2000) [CA 133, 159,577 (2000)].
- 00M123 K. E. Pickerill, J. A. Paladino, and J. J. Schentag, *Pharmacotherapy* **20**, 417 (2000).
- 00M124 X.-H. Peng, M.-J. Wang, Q. Lu, Z.-M. Li, J.-P. Du, and Y. Wang, *Jingxi Huagong* **17**, 325 (2000) [CA 133, 182,909 (2000)].
- 00M125 B. Koppenhoefer, A. Jakob, X. Zhu, and B. Lin, *J. High Resolut. Chromatogr.* **23**, 413 (2000).
- 00M126 L. E. Boccumini, C. L. Fowler, T. A. Campbell, L. F. Puertolas, and K. H. Kaidbey, *Ann. Pharmacother.* **34**, 453 (2000).
- 00M127 Y. Feng, F.-L. Zhao, and S.-Y. Tong, *Fenxi Kexue Xuebao* **16**, 184 (2000) [CA 133, 213,300 (2000)].
- 00M128 K. Takagi, Y. Yajima, and H. Yoshizawa, *Nippon Kagaku Ryoho Gakkai Zasshi* **48**, 633 (2000) [CA 133, 217,260 (2000)].
- 00M129 Y. Ishida, I. Sakurai, H. Okamoto, T. Takashi, M. Morita, and F. Matsumoto, *Nippon Kagaku Ryoho Gakkai Zasshi* **48**, 645 (2000) [CA 133, 217,261 (2000)].
- 00M130 A. S. Amin, *Mikrochim. Acta* **134**, 89 (2000).
- 00M131 S. V. Bel'tyukova, A. V. Egorova, and O. I. Teslyuk, *J. Anal. Chem.* **55**, 682 (2000).
- 00M132 M. Rizk, F. Belal, F. Ibrahim, S. M. Ahmed, and N. M. El-Enany, *Sci. Pharm.* **68**, 173 (2000).
- 00M133 T. Xu, K. Li, Y. Zhan, X. Pan, and G. Rao, *Huaxi Yaoxue Zazhi* **15**, 191 (2000) [CA 133, 275,800 (2000)].
- 00M134 Q.-H. Zhu, Q.-Y. Deng, and L.-M. Zeng, *Zhongshan Daxue Xuebao Ziran Kexueban* **39**, 61 (2000) [CA 133, 301,298 (2000)].
- 00M135 L. Chen, X. Ma, and J. Chen, *Chuangang Jishu Xuebao* **13**, 101 (2000) [CA 133, 301,287 (2000)].
- 00M136 Y. Li, *Guangdong Yaoxueyuan Xuebao* **16**, 215 (2000) [CA 133, 301,310 (2000)].
- 00M137 H. S. Oliveira, M. Goncalo, and A. C. Figueiredo, *Photodermatol., Photoimmunol. Photomed.* **16**, 116 (2000).
- 00M138 S. Navaratman and J. Claridge, *Photochem. Photobiol.* **72**, 283 (2000).
- 00M139 M. Wang, Y. Bai, and E. Du, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 291 (2000) [CA 133, 317,141 (2000)].
- 00M140 J. A. Ocana, M. Callejon, and F. J. Barragan, *Analyst (Cambridge U.K.)* **125**, 2000 (1851).
- 00M141 W. Naixing, M. Quanjie, J. Wei, S. Zhikun, R. Xuezhen, and L. Chuenbo, *J. Indian Chem. Soc.* **77**, 424 (2000).
- 00M142 R. Zhang, J. Lei, R. Li, S. Luo, W. He, H. Cai, and Y. Zhou, *J. Chin. Pharm. Sci.* **9**, 100 (2000) [CA 133, 344,132 (2000)].
- 00M143 X. Yan, D. Gu, X. Hu, G. Cao, X. He, and Y. Song, *Huaxi Yaoxue Zazhi* **15**, 287 (2000) [CA 133, 355,319 (2000)].
- 00M144 H.-R. Park, K.-Y. Chung, H.-C. Lee, J.-K. Lee, and K.-M. Bark, *Bull. Korean Chem. Soc.* **21**, 849 (2000).
- 00M145 X.-Z. Zhang, X.-G. Pan, S.-D. Luo, K. Luo, and X.-L. Shen, *Sepu* **18**, 175 (2000) [CA 133, 37,661 (2000)].
- 00M146 J. Zhang, D. Chen, Y. Yuan, T. Yang, and H. Qu, *Yaoxue Xuebao* **35**, 445 (2000) [CA 133, 95,279 (2000)].

- 00MI47 J. J. Clifford and J. L. Waddington, *Neuropsychopharmacology* **22**, 538 (2000).
- 00MI48 I. Mahmood, *Drug Metab. Drug Interact.* **16**, 143 (2000).
- 00MI49 S. B. Herman, D. M. Juilfs, E. B. Fauman, P. Juneau, and J. P. Menetski, *Mol. Pharmacol.* **57**, 991 (2000).
- 00MI50 M. T. Osinski and K. Schror, *Biochem. Pharmacol.* **60**, 381 (2000).
- 00MI51 R. Kuhn, S. Uckert, C. G. Stief, M. C. Truss, B. Lietz, E. Bischoff, M. Schramm, and U. Jonas, *Urol. Res.* **28**, 110 (2000).
- 00MI52 Y. Guo, S. R. Byrn, and G. Zografi, *Pharm. Res.* **17**, 930 (2000).
- 00MI53 M. Doenhoff, D. Cioli, and G. Kimani, *Parasitol. Today* **16**, 364 (2000).
- 00MI54 M. Ye, H. Zou, Z. Lei, R. Wu, Z. Liu, and J. Ni, *Electrophoresis* **22**, 518 (2000).
- 00MI55 X.-F. Shen, A.-M. Wang, and D.-M. Gao, *Zhongguo Yiyao Gongye Zazhi* **31**, 497 (2000) [*CA* **134**, 227,484 (2001)].
- 00MI56 T. Yamamoro, K. Yashida, and M. Takasugi, *Kagaku Ryoho no Ryoiki* **16**, 1332 (2000) [*CA* **134**, 36,587 (2001)].
- 00MI57 C. Fu, Z. Li, Z. Hong, and S. Liu, *Yaowu Fenxi Zazhi* **20**, 373 (2000) [*CA* **134**, 36,647 (2001)].
- 00MI58 H. Tan, Y. Han, M. Cai, and X. Liu, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 202 (2000) [*CA* **134**, 36,652 (2001)].
- 00MI59 Y. Tu and L. Liu, *Guangpuxue Yu Guangpu Fenxi* **20**, 880 (2000) [*CA* **134**, 46,882 (2001)].
- 00MI60 L. Jia and J.-Q. Zhang, *Fenxi Ceshi Xuebao* **19**, 78 (2000) [*CA* **134**, 76,464 (2001)].
- 00MI61 J. Zhang, J. Chen, and L. Hu, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 373 (2000) [*CA* **134**, 136,567 (2001)].
- 00MI62 T.-W. Yao, S. Zeng, and X. Li, *Zhongguo Yaolixue Yu Dulixue Zazhi* **14**, 268 (2000) [*CA* **134**, 157,161 (2001)].
- 00MI63 Z. Zhang, K. Zhang, and R. Gao, *Yaowu Fenxi Zazhi* **20**, 363 (2000) [*CA* **134**, 198,177 (2001)].
- 00MI64 J. L. Juste Diez de Pinos, M. Adrover Rigo, and J. Ribas Sala, *Farm. Hosp.* **24**, 288 (2000) [*CA* **134**, 202,374 (2001)].
- 00MI65 A. Blotz, L. Michel, A. Moysan, J. Blumel, L. Dubertret, A. H. Ahr, and H.-W. Vohr, *J. Photochem. Photobiol., B* **58**, 46 (2000).
- 00MI66 Y. Zhang, Q. A. Xu, L. A. Trissel, and K. Y. Williams, *Ann. Pharmacother.* **34**, 996 (2000).
- 00MI67 O. I. Teslyuk, S. V. Beltyukova, A. V. Egorova, and I. I. Zheltva, *Zh. Neorg. Khim.* **45**, 2103 (2000) [*CA* **134**, 332,165 (2001)].
- 00MI68 U. P. Halkar and P. B. Ankalkope, *Indian Drugs* **37**, 585 (2000).
- 00MI69 Y.-G. Qian, J. Shang, Q.-L. Li, and Y.-Q. Lu, *Fenxi Shiyanshi* **20**, 83 (2001) [*CA* **134**, 316,252 (2001)].
- 00MI70 A. P. Johnson, *Curr. Opin. Invest. Drugs (Pharma Press Ltd.)* **1**, 52 (2001).
- 00MI71 S. Mill and C. Hootle, *J. Nat. Prod.* **63**, 762 (2000).
- 00MI72 T. He and M. Chen, *Zhongguo Yiyuan Yaoxue Zazhi* **20**, 624 (2000) [*CA* **135**, 28,517 (2000)].
- 00MI73 S. Gupta and M. N. Ansari, *Himalayan Chem. Pharm. Bull.* **17**, 27 (2000) [*CA* **135**, 10,126 (2001)].
- 00MI74 P. Yi, Q. Yu, Z. Shang, and H. Zong, *Yaoxue Xuebao* **35**, 774 (2000) [*CA* **135**, 55,476 (2001)].

- 00MI75 C.-S. Liu, C. Dong, X.-H. Feng, and W.-J. Jin, *Wuhan Daxue Xuebao Ziran Kexueban* **46**, 649 (2000) [*CA* **135**, 97,580 (2001)].
- 00MI76 J. Li, G. Wang, X. Zhang, and S. Zhou, *Zhongguo Yaowu Huaxue Zazhi* **10**, 276 (2000) [*CA* **135**, 107,303 (2001)].
- 00MI77 F. El-Anwar, *J. Drug Res.* **23**, 79 (2000).
- 00MI78 C. Xu, Z. Chen, and L. Hou, *Huaxi Yaoxue Zazhi* **15**, 443 (2000) [*CA* **135**, 308,722 (2001)].
- 00MIP1 R. J. Gillespie, J. Lerpiniere, P. R. Giles, D. R. Adams, L. J. S. Knutsen, and I. A. Cliffe, *PCT Int. Appl.* 00/13,682 (2000) [*CA* **132**, 222,456 (2000)].
- 00MIP2 J. Székely, F. Andrási, Gy. Máté, K. Horváth, E. Horváth, C. Haska-Salamon, P. Arányi, G. Gigler, P. Fekete, and M. Fekete, *PCT Int. Appl.* 00/20,005 (2000) [*CA* **132**, 270,096 (2000)].
- 00MIP3 Y. Fukuda, S. Seto, A. Tanioka, and M. Ikeda, *PCT Int. Appl.* 00/06,578 (2000) [*CA* **132**, 137,397 (2000)].
- 00MIP4 L. Edwards, A. Slassi, A. Tehim, and T. Xin, *PCT Int. Appl.* 00/17,198 (2000) [*CA* **132**, 251,073 (2000)].
- 00MIP5 A. M. M. Mjalli, *PCT Int. Appl.* 00/23,487 (2000) [*CA* **132**, 308,359 (2000)].
- 00MIP6 A. Ejima, S. Ohsuki, H. Ohki, H. Naito, and C. Makino, *PCT Int. Appl.* 00/5230 (2000) [*CA* **132**, 137,383 (2000)].
- 00MIP7 Y. Fukuda, S. Seto, A. Tanioka, and M. Ikeda, *PCT Int. Appl.* 00/6580 (2000) [*CA* **132**, 151,827 (2000)].
- 00MIP8 B. H. Van Lengerich, *PCT Int. Appl.* 00/21,504 (2000) [*CA* **132**, 293,042 (2000)].
- 00MIP9 S. Sawa, *PCT Int. Appl.* 00/16,774 (2000) [*CA* **132**, 241,974 (2000)].
- 00MIP10 K. Hayashi, S. Shimizu, and J. Mitsuyama, *PCT Int. Appl.* 00/46,223 (2000) [*CA* **133**, 150,565 (2000)].
- 00MIP11 Y.-J. Park, H.-S. Lee, M.-H. Kim, and K.-C. Kim, *PCT Int. Appl.* 00/50,428 (2000) [*CA* **133**, 193,174 (2000)].
- 00MIP12 M. Takemura, H. Takahashi, K. Kawakami, T. Takeda, and R. Miyauchi, *PCT Int. Appl.* 00/53,594 (2000) [*CA* **133**, 222,606 (2000)].
- 00MIP13 M. Chrysellis, E. Rekka, and P. Kourounakis, *PCT Int. Appl.* 00/42,030 (2000) [*CA* **133**, 105,045 (2000)].
- 00MIP14 R. A. Mueller, M. L. Bryant, and R. A. Partis, *PCT Int. Appl.* 00/47,198 (2000) [*CA* **133**, 172,150 (2000)].
- 00MIP15 G. M. Bright and K. A. Desai, *PCT Int. Appl.* 00/39,128 (2000) [*CA* **133**, 74,030 (2000)].
- 00MIP16 R. S. Obach, *PCT Int. Appl.* 00/59,486 (2000) [*CA* **133**, 301,178 (2000)].
- 00MIP17 S. B. Christensen IV, M. S. Barnette, and T. J. Torphy, *PCT Int. Appl.* 00/51,598 (2000) [*CA* **133**, 217,702 (2000)].
- 00MIP18 R. Nieman, T. Torphy, and S. Christensen, *PCT Int. Appl.* 00/51,599 (2000) [*CA* **133**, 217,689 (2000)].
- 00MIP19 A. W. Oxford and D. Jack, *PCT Int. Appl.* 00/58,308 (2000) [*CA* **133**, 266,869 (2000)].
- 00MIP20 A. W. Oxford and D. Jack, *PCT Int. Appl.* 00/58,309 (2000) [*CA* **133**, 281,793 (2000)].
- 00MIP21 S. Yin, Faming Zhuanli Shenging Gongkai Shuomingshu 1,273,092 (2000) [*CA* **134**, 344,571 (2001)].

- 00OL581 H. Wamhoff, C. Höhmann, and P. Sohár, *Org. Lett.* **2**, 581 (1999).  
00OL2955 T. Ozawa, S. Aoyagi, and C. Kibayashi, *Org. Lett.* **2**, 2955 (2000).  
00OL4007 D. C. Bland, B. C. Raudenbush, and S. M. Weinreb, *Org. Lett.* **2**, 4007 (2000).  
00SA(A)1787 Z. Liu, Z. Huang, and R. Cai, *Spectrochim. Acta, Part A* **56A**, 1787 (2000).  
00SC2565 S. Agami, C. Kadouri-Puchot, and J.-C. Kizirian, *Synth. Commun.* **30**, 2565 (2000).  
00T233 F. Segat-Dioury, O. Lingibé, B. Graffe, M.-C. Saquet, and G. Lhommet, *Tetrahedron* **56**, 233 (2000).  
00T1005 A. Kilonda, F. Compennolle, K. Peeters, G. J. Joly, S. Toppet, and G. J. Hoornaert, *Tetrahedron* **56**, 1005 (2000).  
00T2469 J. Siró, A. Ramos, J. J. Vaquero, J. Alvarez-Builla, and J. L. García-Navio, *Tetrahedron* **56**, 2469 (2000).  
00TA3913 M. Cellier, Y. Gelas-Mialhe, H.-P. Husson, B. Perrin, and R. Remuson, *Tetrahedron, Asymetry* **11**, 3913 (2000).  
00TAL359 Q. J. Gong, J. L. Qiao, L. M. Du, C. Dong, and W. J. Jin, *Talanta* **53**, 359 (2000).  
00TAL1149 J. A. O. Gonzalez, M. Callejon Mochon, and F. J. B. de la Rosa, *Talanta* **52**, 1149 (2000).  
00TL1205 H. Abe, S. Aoyagi, and C. Kibayashi, *Tetrahedron Lett.* **41**, 1205 (2000).  
00TL1849 I. J. McAlpine and R. W. Armstrong, *Tetrahedron Lett.* **41**, 2000 (1849).  
00UKZ115 S. V. Belyukova, A. V. Egorova, and O. I. Teslyuk, *Ukr. Khim. Zh. (Russ. Ed.)* **66**, 115 (2000).  
00USP6121285 M. Takemura, Y. Kimura, H. Takahashi, K. Kimura, S. Miyauchi, H. Ohki, K. Sugita, and R. Miyauchi, U.S. Pat. 6,121,285 (2000) [CA **133**, 237,871 (2000)].  
00USP6147080 G. W. Bemis, F. G. Salituro, J. P. Duffy, and E. M. Harrington, U.S. Pat. 6,147,080 (2000) [CA **133**, 350,242 (2000)].  
00USP6156753 P. C. Doherty Jr., V. A. Place, and W. L. Smith, U.S. Pat. 6,156,753 (2000) [CA **134**, 25,367 (2001)].  
00ZN(B)1089 I. Wolska and F. Herold, *Z. Naturforsch., B. Chem. Sci.* **55b**, 1089 (2000).  
01AF673 M. Rizk, F. Belal, F. Ibrahim, S. Ahmed, and N. M. El-Enany, *Arzneim.-Forsch.* **51**, 673 (2001).  
01ANC3632 E. M. Golet, A. C. Alder, A. Hartmann, T. A. Ternes, and W. Giger, *Anal. Chem.* **73**, 3632 (2001).  
01BCJ1261 P. Djurdjevic, M. Jelkic-Stankov, and I. Lazarovic, *Bull. Chem. Soc. Jpn.* **74**, 1261 (2001).  
01CHE382 A. V. Borisov, T. V. Goncharova, G. N. Borisova, V. K. Osmanov, and Zn.V. Matsulevich, *Chem. Heterocycl. Compd. (Engl. Transl.)* **37**, 382 (2001).  
01CPH77 B. Lévy, A. Kotschy, and D. M. Smith, *Chem. Phys.* **266**, 77 (2001).  
01EJOC987 T. Renaud, J.-P. Hurvois, and P. Uriac, *Eur. J. Org. Chem.*, 987 (2001).  
01EJOC2385 C. Agami, F. Bisaro, S. Comesse, S. Guesné, C. Kadouri-Puchot, and R. Morgentin, *Eur. J. Org. Chem.*, 2385 (2001).  
01EUP1074257 K. A. Desai, A. F. J. Fliri, and M. A. Sanner, Eur. Pat. Appl. 1,074,257 (2001) [CA **134**, 163,060 (2001)].

- 01EUP1099442 G. Chang and J. Vincent, Eur. Pat. Appl. 1,099,442 (2001) [*CA* **134**, 348,283 (2001)].
- 01GEP19935209 M. C. Truss, C. G. Stief, U. Jonas, S. Ückert, A. J. Becker, and W.-G. Forssmann, Ger. Offen 19,935,209 (2001) [*CA* **134**, 157,586 (2001)].
- 01JA315 K. M. Bertini Gross and P. Beak, *J. Am. Chem. Soc.* **123**, 315 (2001).
- 01JA8851 G. R. Heintzelman, W.-K. Fang, S. P. Keen, G. A. Wallace, and S. M. Weinreb, *J. Am. Chem. Soc.* **123**, 8851 (2001).
- 01JAP(K)01/31654 H. Nakamura, S. Yokota, I. Umezawa, and T. Inoue, Jpn. Kokai Tokkyo Koho 01/31,654 (2001) [*CA* **134**, 147,504 (2001)].
- 01JAP(K)01/48807 S. Suzuki, H. Ogawa, and M. Takeuchi, Jpn. Kokai Tokkyo Koho 01/48,807 (2001) [*CA* **134**, 183,485 (2001)].
- 01JAP(K)01/139577 M. Tani, H. Kobayashi, N. Miike, K. Nagase, T. Yaguchi, and T. Sasaki, Jpn. Kokai Tokkyo Koho 01/139,577 (2001) [*CA* **134**, 352,364 (2001)].
- 01JAP(K)01/172283 S. Noguchi and Y. Yokoyama, Jpn. Kokai Tokkyo Koho 01/172,283 (2001) [*CA* **135**, 61,344 (2001)].
- 01JAP(K)01/213878 F. Ito, H. Noguchi, Y. Ohashi, and H. Shimokawa, Jpn. Kokai Tokkyo Koho 01/213,878 (2001) [*CA* **135**, 152,805 (2001)].
- 01JBC11559 R. Zoraghi, S. Kunz, K. Gong, and T. Seebeck, *J. Biol. Chem.* **276**, 11,559 (2001).
- 01JC(A)249 T. Christians and U. Holzgrabe, *J. Chromatogr. A* **911**, 249 (2001).
- 01JC(B)91 C. Immanuel and A. K. Hemanth Kumar, *J. Chromatogr. B* **760**, 91 (2001).
- 01JC(B)169 C. Horskötter and G. Blaschke, *J. Chromatogr. B* **754**, 169 (2001).
- 01JC(B)311 C. Maraschiello, E. Cusidó, M. Abellán, and J. Vilageliu, *J. Chromatogr. B* **754**, 311 (2001).
- 01JHC205 Th. Billert, R. Beckert, M. Döring, J. Wuckelt, P. Fehling, and H. Görls, *J. Heterocycl. Chem.* **38**, 205 (2001).
- 01JLC1115 P. S. Bonato, V. A. P. Jabor, F. O. Paías, and V. L. Lanchote, *J. Liq. Chromatogr. Relat. Technol.* **24**, 1115 (2001).
- 01JMC186 M. L. López-Rodríguez, M. J. Morcillo, E. Fernández, L. Orensanz, M. E. Beneytez, J. Manzanares, and J. A. Fuentes, *J. Med. Chem.* **44**, 186 (2001).
- 01JMC198 M. L. López-Rodríguez, M. J. Morcillo, E. Farnández, G. Porras, M. L. Rosado, L. Pardo, and K.-J. Schaper, *J. Med. Chem.* **44**, 198 (2001).
- 01JMC1011 P. Molina, E. Aller, Á. Lorenzo, P. López-Cremades, I. Rioja, A. Ubeda, M. C. Terencio, and M. J. Alcaraz, *J. Med. Chem.* **44**, 1011 (2001).
- 01JMC2219 J. M. Bartolomé-Nebreda, R. Patino-Molina, M. Martín-Martínez, I. Gómez-Monterrey, M. T. García-López, R. González-Muniz, E. Cenarruzabeitia, M. Latorre, J. Del Rio, R. Herranz, *J. Med. Chem.* **44**, 2219 (2001).
- 01JOC3338 T. Ozawa, S. Aoyagi, and C. Kibayashi, *J. Org. Chem.* **66**, 3338 (2001).
- 01JPS749 Y. H. Zhao, J. Le, M. H. Abraham, A. Hersey, P. J. Eddershaw, C. N. Luscombe, D. Boutina, G. Beck, B. Sherborne, I. Cooper, J. A. Platts, *J. Pharm. Sci.* **90**, 747 (2001).
- 01MI1 X. Nie, S. Luo, and X. Cheng, *Zhongguo Yiyuan Yaoxue Zazhi* **21**, 86 (2001) [*CA* **134**, 271,357 (2001)].

- 01MI2 J. Barbosa, D. Barrón, J. Cano, E. Jiménez-Lozano, V. Sanz-Nebot, and I. Toro, *J. Pharm. Biomed. Anal.* **24**, 1087 (2001).
- 01MI3 J. De Lu, W. Yuan, and X. Y. Fu, *Chin. Chem. Lett.* **12**, 155 (2001) [*CA* **134**, 275,115 (2001)].
- 01MI4 W. Li, J. Chen, B.-R. Xiang, and D.-K. An, *Huaxue Xuebao* **59**, 109 (2001) [*CA* **134**, 277,504 (2001)].
- 01MI5 J. Sunderland, C. M. Tobin, A. J. Hedges, A. P. MacGowan, and L. O. White, *J. Antimicrob. Chemother.* **47**, 271 (2001).
- 01MI6 X. Bao, *Guangpu Shiyanshi* **18**, 265 (2001) [*CA* **134**, 344,666 (2001)].
- 01MI7 C. N. Alves, O. A. S. Romero, and A. B. F. da Silva, *J. Mol. Struct. (Theochem)* **535**, 165 (2001).
- 01MI8 A. Radi and A. M. Hassanein, *Chem. Anal. (Warsaw. Pol.)* **46**, 561 (2001).
- 01MI9 Y. Mitsui and K. Arizono, *Int. J. Parasitol.* **31**, 87 (2001).
- 01MI10 J. Liu and H. Zhao, *Fenxi Ceshi Xuebao* **20**, 77 (2001) [*CA* **135**, 164,301 (2001)].
- 01MI11 H. Gao, Y. Zeng, and E. Cao, *Beijing Shifan Daxue Xuebao Ziran Kexueban* **37**, 233 (2001) [*CA* **135**, 262,363 (2001)].
- 01MI12 V. A. P. Jabor and P. S. Bonato, *Electrophoresis* **22**, 1399 (2001).
- 01MI13 N. Srivastava, *Orient. J. Chem.* **17**, 156 (2001) [*CA* **135**, 210,995 (2001)].
- 01MI14 L. J. V. Piddock, Y. F. Jin, and D. J. Griggs, *J. Antimicrob. Chemother.* **47**, 261 (2001).
- 01MI15 E. Filippini, G. Cruciani, O. Tabarrini, V. Cecchetti, and A. Fravolini, *J. Comput.-Aided Mol. Des.* **15**, 203 (2001).
- 01MI16 S. Sauvaigo, T. Douki, F. Odin, S. Caillat, J.-L. Ravanat, and J. Cadet, *Photochem. Photobiol.* **73**, 230 (2001).
- 01MI17 S. Bottcher, H. von Baum, T. Hoppe-Tichy, C. Benz, and H.-G. Sonntag, *J. Pharm. Biomed. Anal.* **25**, 197 (2001).
- 01MI18 Y. Qian, Y. Lu, J. Hu, Y. Mao, and Q. Li, *Yaoxue Xuebao* **36**, 137 (2001) [*CA* **135**, 112,096 (2001)].
- 01MI19 T. De Boer, R. Mol, R. A. De Zeeuw, G. J. De Jong, and K. Ensing, *Electrophoresis* **22**, 1413 (2001).
- 01MI20 X. Huang, L. Fang, J. Xu, F. You, and X. Zeng, *Zhongguo Yaoxue-Zazhi (Beijing China)* **36**, 194 (2001) [*CA* **135**, 146,730 (2001)].
- 01MI21 S. E. Berning, *Drugs* **61**, 9 (2001).
- 01MI22 M. Gandhimathi, G. Vani, K. Vikram, and T. K. Ravi, *East. Pharm.* **44**, 137 (2001).
- 01MI23 S. Monti, S. Sortino, E. Fasini, and A. Albini, *Chem.-Eur. J.* **7**, 2185 (2001).
- 01MI24 S. J. Martin, R. Jung, and C. G. Garvin, *Drug Saf.* **24**, 199 (2001).
- 01MI25 S.-Y. Lee, B.-H. Min, S.-W. Song, S.-Y. Oh, S.-M. Lim, S.-L. Kim, and D.-I. Kim, *Biotechnol. Bioprocess Eng.* **6**, 179 (2001).
- 01MI26 W. Wang, J. Lu, X. Fu, and Y. Chen, *Anal. Lett.* **34**, 569 (2001).
- 01MI27 A. Aminimanizani, P. Beringer, and R. Jelliffe, *Clin. Pharmacokinet.* **40**, 169 (2001).
- 01MI28 A. I. Azcurra, L. M. Yudi, A. M. Baruzzi, and T. Kakiuchi, *J. Electroanal. Chem.* **506**, 138 (2001).
- 01MI29 P. Yi, Z. Shang, and Q. Yu, *Fenxi Huaxue* **29**, 646 (2001) [*CA* **135**, 282,728 (2001)].

- 01MI30 M. Kobayashi, N. Sada, M. Sugawara, K. Iseki, and K. Miyazaki, *Int. J. Pharm.* **221**, 87 (2001).
- 01MI31 R. A. Press, *Pharmacotherapy* **21** (7, Pt 2), 1005 (2001).
- 01MI32 S.-Y. Lee, B.-H. Min, S.-H. Hwang, Y.-M. Koo, C.-K. Lee, S.-W. Song, S.-Y. Oh, S.-M. Lim, S.-L. Kim, D.-I. Kim, *Biotechnol. Lett.* **23**, 1033 (2001).
- 01MI33 G. H. Ross, D. H. Wright, K. H. Ibrahim, B. W. Gunderson, and J. C. Rotschafer, *J. Infect. Dis. Pharmacother.* **4**, 47 (2001).
- 01MI34 Q. Gong, L. Du, W. Jin, C. Dong, and C. Liu, *Guangpuxue Yu Guangpu Fenxi* **21**, 356 (2001) [*CA* **135**, 352,290 (2001)].
- 01MI35 Z. Zang, D. Chen, Z. Xin, W. Zhu, and X. He, *Zhongguo Kangshengsu Zazhi* **26**, 230 (2001) [*CA* **135**, 362,692 (2001)].
- 01MI36 X. Wang, *Zhongguo Yiyao Gongye Zazhi* **32**, 260 (2001) [*CA* **135**, 376,911 (2001)].
- 01MI37 A. S. Amin, M. E. Moustafa, H. A. Dessouki, and A. Abd-Allah, *Quin. Anal. (Barcelona Spain)* **20**, 93 (2001) [*CA* **135**, 322,807 (2001)].
- 01MIP1 R. Higuchi, K. L. Arienti, M. Neelakandha, B. Pio, L. Zhi, P. Chen, and T. R. Caferro, PCT Int. Appl. 01/16,139 (2001) [*CA* **134**, 222,717 (2001)].
- 01MIP2 S. R. Turner and S. Thaisrivongs, PCT Int. Appl. 01/25,239 (2001) [*CA* **134**, 280,849 (2001)].
- 01MIP3 Y. Han, A. Giroux, R. Zamboni, D. J. McKay, C. I. Bayly, E. L. Grimm, and J. Colucci, PCT Int. Appl. 01/05,772 [*CA* **134**, 115,970 (2001)].
- 01MIP4 C. Hulme, G. C. Morton, J. M. Salvino, R. F. Labaudiniere, H. J. Mason, M. M. Morrisette, L. Ma, and M.-P. Cherrier, PCT Int. Appl. 01/10,799 (2001) [*CA* **134**, 178,141 (2001)].
- 01MIP5 T. Xin, M. Isaac, and A. Slassi, PCT Int. Appl. 01/32,660 (2001) [*CA* **134**, 353,322 (2001)].
- 01MIP6 L. Edwards, M. Isaac, S. Maddaford, A. Slassi, and T. Xin, PCT Int. Appl. 01/05,758 (2001) [*CA* **134**, 131,423 (2001)].
- 01MIP7 R. Leger, W. J. Watkins, J. Z. Zhang, T. E. Renau, V. J. Lee, T. Ohta, K. Nakayama, Y. Ishida, M. Ohtsuka, and H. Kawato, PCT Int. Appl. 01/30,757 (2001) [*CA* **134**, 336,205 (2001)].
- 01MIP8 E. Jefferson and E. E. Swayze, PCT Int. Appl. 01/14,346 (2001) [*CA* **134**, 193,744 (2001)].
- 01MIP9 P. Snyder, PCT Int. Appl. 01/35,979 (2001) [*CA* **134**, 361,385 (2001)].
- 01MIP10 K. Sato, Y. Takayanagi, K. Okano, K. Nakayama, A. Imura, M. Itoh, T. Yagi, Y. Kobayashi, and T. Nagai, PCT Int. Appl. 01/18,005 (2001) [*CA* **134**, 222,719 (2001)].
- 01MIP11 S.-T. Hong, S.-J. Lee, W.-G. Kho, and J.-C. Joo, PCT Int. Appl. 01/49,269 (2001) [*CA* **135**, 97,476 (2001)].
- 01MIP12 S. Seto, Y. Fukuda, S. Izawa, M. Ideda, and A. Tanioka, PCT Int. Appl. 01/85,732 (2001) [*CA* **135**, 357,947 (2001)].
- 01MIP13 S. Abdul-Rahman, PCT Int. Appl. 01/36,408 (2001) [*CA* **135**, 5534 (2001)].
- 01MIP14 P. Del Soldato, F. Benedini, and P. Antognazza, PCT Int. Appl. 01/54,691 (2001) [*CA* **135**, 152,367 (2001)].
- 01MIP15 R. Mihalik, PCT Int. Appl. 01/60,380 (2001) [*CA* **135**, 185,477 (2001)].

- 01MIP16 H.-H. Schulz and G. Schlimbach, PCT Int. Appl. 01/45,679 (2001) [*CA* **135**, 71,252 (2001)].
- 01MIP17 M. Takemura, H. Takahashi, K. Kawakami, K. Namba, and M. Tanaka, PCT Int. Appl. 01/58,876 (2001) [*CA* **135**, 180,773 (2001)].
- 01MIP18 Y. Cheng and J. Manwell, PCT Int. Appl. 01/40,224 (2001) [*CA* **135**, 33,488 (2001)].
- 01MIP19 B. L. Palucki, K. J. Barakat, L. Guo, Y. Lai, R. P. Nargund, M. K. Park, P. G. Pollard, I. K. Sebhat, and Z. Ye, PCT Int. Appl. 01/70,708 (2001) [*CA* **135**, 272,990 (2001)].
- 01MIP20 M. H. Block and P. Schofield, PCT Int. Appl. 01/85,730 (2001) [*CA* **135**, 371,763 (2001)].
- 01MIP21 P. C. Doherty, Jr., V. A. Place, and W. L. Smith, PCT Int. Appl. 01/41,807 (2001) [*CA* **135**, 51,053 (2001)].
- 01MIP22 S. Masumoto, M. Kitano, and N. Ohashi, PCT Int. Appl. 01/79,206 (2001) [*CA* **135**, 331,436 (2001)].
- 01MIP23 P. Bird, E. L. Ellsworth, D. Q. Nguyen, J. P. Sanchez, H. D. H. Showalter, R. Singh, M. A. Stier, T. P. Tran, B. M. Watson, and J. Yip, PCT Int. Appl. 01/53,273 (2001) [*CA* **135**, 122,511 (2001)].
- 01OL997 A. Zawadzka, A. Leniewski, J. K. Maurin, K. Wojtasiewicz, and Z. Czarnocki, *Org. Lett.* **3**, 997 (2001).
- 01PHA146 E.-J. Kim, W. Hänsel, and D. Heber, *Pharmazie* **56**, 146 (2001).
- 01SA(A)1317 S. Wu, W. Zhang, X. Chen, Z. Hu, M. Hooper, B. Hooper, and Z. Zhao, *Spectrochim. Acta, Part A* **57A**, 1317 (2001).
- 01SL833 D. Edmont and J. Chenault, *Synlett*, 833 (2001).
- 01TAL885 F. A. Aly, S. A. Al-Tamimi, and A. A. Alwarthan, *Talanta* **53**, 885 (2001).
- 01TL543 B. Herberich, M. Kinugawa, A. Vazquez, and R. M. Williams, *Tetrahedron Lett.* **42**, 543 (2001).
- 01TL4621 B. Lebrun, J.-C. Brackman, D. Daloze, P. Kalushkov, and J. M. Pasteels, *Tetrahedron Lett.* **42**, 4621 (2001).
- 01USP6169086 A. Ejima, S. Ohsuki, H. Ohki, and H. Naito, U.S. Patent 6,169,086 (2001) [*CA* **134**, 86,238 (2001)].
- 01USP6251893 S. Maddaford, T. Xin, A. Slassi, A. Tehin, and Q. Qizo, U.S. Pat. 6,251,893 (2001) [*CA* **135**, 61,353 (2001)].
- 01YZ319 M. Kudo, T. Ohkubo, and K. Sugawara, *Yakugaku Zasshi* **121**, 319 (2001) [*CA* **135**, 146,726 (2001)].